E06/93

PRACTICE OF MEDICINE

VOLUME VIII

PRACTICE OF MEDICINE

EDITED BY

FREDERICK TICE, M.D.

PROFESSOR OF MEDICINE AND CLINICAL MEDICINE, AND
HEAD OF THE DEPARTMENT OF MEDICINE,
UNIVERSITY OF ILLINOIS, COLLEGE
OF MEDICINE

VOLUME VIII

HAGERSTOWN, MARYLAND
W. F. PRIOR COMPANY, INC.
1924

Printed in the United States of America

CONTENTS

VOLUME VIII

SECTION XI: DISEASES DUE TO INTOXICATIONS

CHAPTER PAGE

I. ALCOHOLISM 1

By Stephen Perham Jewett

General Consideration 1
Causes for Excessive Drinking 4
  Personal Condition 4
  Social Conditions 4
Physiological Effects of Alcohol 5
Pathological Changes Due to Alcohol 5
Forms of Alcoholism 6
  Acute Alcoholic Intoxication 6
    Symptomatology 6
    Diagnosis 6
    Treatment 6
  Chronic Alcoholic Poisoning 6
    Symptomatology 6
    Treatment 7
    Prognosis 8
Characteristic Clinical Forms of Alcoholism 9
  Pathological Intoxication 9
  Delirium Tremens 9
    Etiology 9
    Symptomatology 10
    Clinical Varieties 10
    Treatment 11
    Pathology 12
  Acute Hallucinosis 12
  Acute Paranoid Form 13
  Chronic Paranoid Form 13
  Korsakow's Disease 14
  Alcoholic Deterioration or Dementia 14
Other Less Characteristic Types 15
  Pseudoparesis 15
  Alcoholic Epilepsy 15
  Alcoholic Polyneuritis 15
  Pseudotabes 16
  Alcoholic "Wet Brain" or Alcoholic "Meningitis" 16
    Symptomatology 16
    Treatment 16
    Prognosis 16

CHAPTER PAGE

II. DRUG ADDICTION 17

By Stephen Perham Jewett

Opium and Its Derivatives 18
  General Considerations 18
    Opium Addiction 18
    Morphin Addiction 19
    Heroin Addiction 19
    Laudanum Addiction 20
    Paregoric Addiction 20
  Etiology 20
    Predisposing Causes 20
  Symptomatology 25
    Poisoning by Opium and Its Derivatives 25
  Diagnosis 29
  Treatment 30
    General Principles and Considerations 30
    Drugs Useful during Withdrawal Period 36
    Case Histories and Clinical Notes 37
  Prognosis 51
  Pathology 52
Cocain Addiction 53
  Etiology 53
  Symptomatology 53
    Physiological Effects 53
    Psychological Effects 53
  Treatment 54
  Prognosis 54
Paraldehyd Habit 55
  Symptomatology 55
  Treatment 56
Bromid Habit 56
  Symptomatology 56
  Treatment 57
Chloralism 57
  Symptomatology 57
  Treatment 57
Addiction to Other Drugs 57

III. LEAD-POISONING 59

By Tasker Howard

Acute Lead-Poisoning 59
Chronic Lead-Poisoning 59
  Etiology 59
    Predisposing Factors 59
    Toxicity of Various Salts of Lead 62
    Modes of Entering the System 62
  Symptomatology 62
    Period of Development 62
    Course 63
  Diagnosis 67
    Differential Diagnosis 67
  Association with Other Diseases 68
  Treatment 68
    Prophylaxis 68
    General Management 68
    Medicinal Treatment 69
    Symptomatic Treatment 70
  Prognosis 71

CHAPTER PAGE
- Pathology . . . 72
- Historical Summary and Distribution . . . 73

IV. MERCURY-POISONING . . . 75

By Tasker Howard

- Etiology . . . 75
- Acute Mercurial Poisoning . . . 76
  - Acute Bichlorid-poisoning . . . 76
    - Symptomatology . . . 76
    - Diagnosis . . . 77
    - Treatment . . . 78
    - Pathology . . . 79
- Chronic Mercurial Poisoning . . . 79
  - Symptomatology . . . 79
  - Diagnosis . . . 80
  - Treatment . . . 80
    - Prophylaxis . . . 80
    - General Treatment . . . 80
  - Prognosis . . . 81
  - Pathology . . . 81

V. ARSENIC-POISONING . . . 83

By Tasker Howard

- General Etiology . . . 83
  - Occupation . . . 83
  - Volatile Arsenical Compounds . . . 83
  - Arsenic in Food . . . 83
  - Overdoses of Arsenic Used as a Medicine . . . 84
- Acute Arsenic-poisoning . . . 84
  - Symptomatology . . . 84
  - Diagnosis . . . 84
  - Treatment . . . 85
  - Prognosis . . . 85
  - Pathology . . . 85
- Chronic Arsenic-poisoning . . . 86
  - Symptomatology . . . 86
    - General Symptoms . . . 86
  - Diagnosis . . . 87
  - Treatment . . . 88
  - Prognosis . . . 88
  - Pathology . . . 88

VI. FOOD-POISONING . . . 89

By Seale Harris

- Definition . . . 89
- Etiology . . . 91
  - Exciting Cause . . . 91
  - Causes Other than Specific Organisms . . . 102
    - Poisonous Plants . . . 102
    - Chemical Impurities in Food . . . 104
  - Food Preservatives . . . 106
  - Food Substitutes . . . 107
  - German Literature on Food-poisoning . . . 109
- Food Idiosyncrasies . . . 109
- Symptomatology . . . 111
  - Clinical History . . . 112
    - Mode of Onset . . . 112

CHAPTER PAGE
Diagnosis 114
Pathology 115
Bacteriological Examinations 115
Treatment 117
Prophylaxis 117

VII. MILK-SICKNESS 123
By Arthur J. Clay
Definition 123
Etiology 123
Predisposing Factors 123
Exciting Cause 125
Symptomatology 126
Intoxication 126
Symptoms and Signs in Animals 126
Symptoms and Physical Signs in Man 128
Diagnosis 129
Differential 129
Clinical 129
Laboratory 129
Treatment 130
Prophylaxis 130
Medicinal Treatment 130
Prognosis 130
Pathology 130

SECTION XII: DISEASES OF THE ENDOCRINE GLANDS

I. DISORDERS OF THE ADRENALS, THYMUS, PINEAL, OVARIES AND TESTICLES 131
Louis T. de M. Sajous
Diseases of the Adrenals 132
General Anatomy and Physiology 132
Functional Hypoadrenia 141
Symptomatology and Etiology 141
Diagnosis 147
Treatment 147
Prophylaxis 147
Curative Treatment 148
Pathology 149
Terminal Hypoadrenia 150
Symptomatology and Etiology 150
Association with Other Diseases 151
Diagnosis 152
Treatment 152
Pathology 154
Addison's Disease 154
Etiology 154
Symptomatology 155
Diagnosis 157
Treatment 157
Prognosis 159

PAGE
Hyperadrenia and Adrenal Hemorrhage 159
  Etiology 159
  Symptomatology 160
  Diagnosis 160
  Treatment 161
  Pathology 161
Hematoma of the Adrenals 161
  Etiology 161
  Symptomatology 161
  Diagnosis 162
  Treatment 162
  Pathology 162
Hypernephroma 162
  Symptomatology 162
  Diagnosis 163
  Treatment 163
  Pathology 163
Tumors of the Adrenals 164
 Malignant Tumors 164
  Symptomatology 164
  Diagnosis 164
  Treatment 165
 Benign Tumors 165
  Symptomatology 165
  Diagnosis 165
  Treatment 165
Diseases of the Thymus 165
  General Anatomy and Physiology 165
 Thymus Insufficiency 167
 Mongolian Idiocy 169
  Etiology 169
  Symptomatology 169
  Treatment 169
  Pathology 170
 Thymus in Backward Children 170
  Etiology 170
  Treatment 170
 Thymus Hypertrophy 171
  Etiology and Pathogenesis 171
  Symptomatology 172
  Diagnosis 173
  Treatment 174
  Pathology 175
Diseases of the Pineal Gland 176
  General Anatomy and Physiology 176
 Tumors of the Pineal Body 177
 Pineal Insufficiency in Backward Children 178
Endocrinic Disorders of the Ovaries 178
  General Anatomy and Physiology 178
 Endocrinic Ovarian Insufficiency 180
  Etiology 180
  Symptomatology 181
  Diagnosis 182
  Treatment 182
 Endocrinic Ovarian Overactivity 184
  Symptomatology 184
  Treatment 184
Endocrinic Disorders of the Testicles 185
  General Anatomy and Physiology 185

CHAPTER PAGE
Endocrinic Testicular Insufficiency 186
Etiology 186
Symptomatology 186
Treatment 187
Endocrinic Testicular Overactivity 188

II. DISEASES OF THE THYROID AND PARATHYROID GLANDS 197

By Charles E. de M. Sajous

Functions of the Thyroid Gland and Parathyroid Glandules 197
Functions of the Parathyroids 201
Goiter 204
Etiology and Pathogenesis 204
Symptomatology 208
Non-Toxic Goiter 210
Types and Prognosis 210
Non-Toxic Parenchymatous Goiter 210
Non-Toxic Nodular Goiter 211
Pressure Symptoms 212
Non-Toxic Goiter Heart 213
Treatment 213
Prophylaxis 213
General Measures 215
Curative Treatment 216
Pathology 218
Geographical Distribution 219
Accessory Non-Toxic Goiters 221
Symptomatology 221
Treatment 222
Malignant Goiter 222
Symptomatology 222
Treatment 222
Thyroiditis and Strumitis 223
Symptomatology 223
Treatment 224
Hyperthyroidia or Hyperthyroidism 225
Etiology and Pathogenesis 225
Toxemia Genesis 225
Psychoneural Genesis 227
Symptomatology 231
Clinical History 231
Course of the Disease 233
Diagnosis 239
Complications 241
The Thymus as a Complicating Factor 241
Treatment 242
Toxemic Group 242
Neurogenic Group 246
Pathology 251
Prognosis 253
Cretinism 254
Definition 254
Etiology and Pathogenesis 254
Symptomatology 255
Diagnosis 258
Treatment 259
Pathology 261

CHAPTER PAGE
Myxedema or Progressive Hypothyroidism . . . 261
  Definition . . . 261
  Etiology and Pathogenesis . . . 261
  Symptomatology . . . 262
  Treatment . . . 262
Hypothyroidism or Larval Myxedema . . . 263
  Definition . . . 263
  Etiology and Pathogenesis . . . 263
  Symptomatology . . . 264
  Treatment . . . 265
Hypoparathyroidia or Parathyroid Tetany . . . 265
  Etiology and Pathogenesis . . . 265
  Symptomatology . . . 266
  Treatment . . . 267

III. DISEASES OF SPLEEN . . . 273
By C. H. Bunting
  Introduction . . . 273
  Anatomy of the Spleen . . . 274
  Physiology . . . 275
  Splenectomy . . . 277
Abnormalities . . . 280
 Abnormalities of Size and Shape . . . 280
 Abnormalities of Position . . . 281
  Congenital Displacement . . . 281
  Acquired Displacement . . . 281
   Etiology . . . 281
   Symptomatology . . . 281
    General Symptoms . . . 281
    Physical Findings . . . 282
    Laboratory Findings . . . 282
   Diagnosis . . . 282
   Complications . . . 282
   Treatment . . . 282
   Prognosis . . . 282
   Pathology . . . 282
 Traumatic Lesions . . . 282
  Wounds . . . 283
  Contusion . . . 283
   Etiology . . . 283
   Symptomatology . . . 283
   Diagnosis . . . 283
   Complications and Sequelæ . . . 283
   Treatment . . . 283
   Prognosis . . . 283
   Pathology . . . 283
 Rupture of the Spleen . . . 284
   Etiology . . . 284
   Symptomatology . . . 284
   Diagnosis . . . 284
   Complications . . . 284
   Sequelæ . . . 285
   Treatment . . . 285
   Prognosis . . . 285
   Pathology . . . 285
 Vascular Lesions . . . 285
  Chronic Passive Congestion . . . 285
  Hemorrhage . . . 286

PAGE
Infarct of the Spleen . . . 286
  Etiology . . . 286
  Symptomatology . . . 286
  Complications and Sequelæ . . . 287
  Treatment . . . 287
  Prognosis . . . 287
  Pathology . . . 287
Degenerations . . . 287
 Amyloid Infiltration . . . 287
  Etiology . . . 287
  Symptomatology . . . 288
  Treatment . . . 288
  Prognosis . . . 288
  Pathology . . . 288
Inflammations of the Spleen . . . 288
 Abscess of the Spleen . . . 289
  Etiology . . . 289
  Symptomatology . . . 289
  Diagnosis . . . 289
  Complications . . . 289
  Treatment . . . 290
  Prognosis . . . 290
  Pathology . . . 290
 Tuberculosis of the Spleen . . . 290
  Etiology . . . 290
  Symptomatology . . . 290
  Diagnosis . . . 291
  Complications . . . 291
  Treatment . . . 291
  Prognosis . . . 291
  Pathology . . . 291
 Syphilis . . . 291
Tumors of the Spleen . . . 292
 Acute Splenic Tumor . . . 292
 Chronic Splenic Tumors . . . 293
  Splenomegaly of the Banti Type . . . 293
   Etiology . . . 294
   Symptomatology . . . 294
   Diagnosis . . . 295
   Complications . . . 295
   Treatment . . . 295
   Prognosis . . . 295
   Pathology . . . 296
  Gaucher's Splenomegaly . . . 296
  Tropical Febrile Splenomegaly . . . 296
   Etiology . . . 296
   Symptomatology . . . 296
   Diagnosis . . . 297
   Complications . . . 297
   Treatment . . . 297
   Prognosis . . . 298
   Pathology . . . 298
  Infantile Kala-Azar . . . 298
  Histoplasmosis . . . 298
  Cysts of the Spleen . . . 299
   Etiology . . . 299
   Symptomatology . . . 299
   Diagnosis . . . 299
   Complications . . . 299

CHAPTER PAGE

Treatment 299
Prognosis 299
Pathology 300
New Growths 300

IV. GAUCHER'S DISEASE 305
By N. E. Brill and F. S. Mandlebaum

Introduction 305
Definition 306
Etiology 306
  Predisposing Causes 306
Symptomatology 307
  Mode of Onset 307
  Objective Symptoms 307
Diagnosis 313
  Differential Diagnosis 313
Complications 317
Treatment 317
Prognosis 318
  Duration and Termination 318
Pathology 318
  Spleen 319
  Liver 322
  Lymph-nodes 324
  Bone-marrow 326
  Other Organs 327
  Pathological Conditions Simulating Gaucher's Disease . 328
Historical Summary 328

V. DISORDERS OF THE PITUITARY GLAND 337
By William Engelbach and John L. Tierney

Lobar Function Classification 337
Anatomical Consideration of Individual Lobes 340
Clinical Types 346
Hypopituitarism 347
  Pituitary Amenorrhea 347
    Etiology 347
    Symptomatology 347
    Treatment 365
    Prognosis 366
    Pathology 367
  Pituitary Metrorrhagia 371
    Etiology 371
    Symptomatology 371
    Diagnosis 374
    Complications, Sequelæ and Associated Diseases . . . 376
    Clinical Varieties 377
    Treatment 378
    Prognosis 380
    Pathology 380
  Pituitary Dysmenorrhea 385
    Etiology 385
    Symptomatology 385
    Diagnosis 391
    Complications, Sequelæ and Associated Diseases . . . 393
    Clinical Varieties 393
    Treatment 394

PAGE
Prognosis 395
Pathology 395
Case IV 395
Etiology 395
Symptomatology 396
Diagnosis 400
Complications and Sequelæ 403
Clinical Varieties 403
Treatment, Prognosis and Pathology 403
Pituitary Tumor 405
Posterior Lobe Insufficiency, Pre-adolescent Neoplastic Type . 405
Etiology 405
Symptomatology 405
Diagnosis 409
Complications and Sequelæ 411
Clinical Varieties and Types 412
Treatment 419
Prognosis 419
Pathology 420
Posterior Lobe Insufficiency, Postadolescent Neoplastic Type 420
Etiology 420
Symptomatology 421
Complications 437
Sequelæ 438
Association of Other Diseases 438
Clinical Varieties 439
Treatment 440
Prognosis 440
Pathology 441
Pituitary Obesity 445
Bilobar Insufficiency of the Pre-adolescent, Aneoplastic Type 445
Etiology 445
Symptomatology 445
Diagnosis 452
Complications 459
Associated Diseases 460
Clinical Varieties 461
Treatment 465
Prognosis 469
Pathology 469
Bilobar Insufficiency of the Postadolescent, Aneoplastic Type 470
Etiology 470
Symptomatology 470
Diagnosis 477
Complications, Sequelæ and Associated Diseases . . . 479
Clinical Varieties 479
Treatment, Prognosis and Pathology 483
Pituitary Headache 485
Etiology 485
Symptomatology 485
Diagnosis 489
Complications and Sequelæ 491
Clinical Varieties 491
Treatment 493
Prognosis 494
Pathology 494
Pituitarism with Marked Abdominal Pain 497
Etiology 497
Symptomatology 498

PAGE
    - Diagnosis 509
    - Complications and Sequelæ 513
    - Associated Diseases 513
    - Adolescent Hypopituitarism 514
    - Adolescent Pituitarism 517
    - Treatment 518
    - Prognosis 520
    - Pathology 521
  - Pituitarism with Marked Constitutional Symptoms 523
    - Etiology 523
    - Symptomatology 523
    - Diagnosis 539
    - Complications and Sequelæ 541
    - Associated Diseases 542
    - Clinical Varieties 543
    - Treatment 543
    - Prognosis 549
    - Pathology 549
  - Pituitary Epilepsy 553
    - Etiology 553
    - Symptomatology 553
    - Diagnosis 573
    - Complications and Sequelæ 580
    - Associated Diseases 580
    - Clinical Varieties 581
    - Treatment 582
    - Prognosis 583
    - Pathology 583
  - Pituitary Somnolence or Hibernation 587
    - Etiology 587
    - Symptomatology 587
    - Diagnosis 593
    - Complications, Sequelæ and Associated Diseases 596
    - Clinical Varieties 596
    - Treatment 598
    - Prognosis 601
    - Pathology 601
- Hyperpituitarism 607
  - Gigantism 607
    - Etiology 607
    - Symptomatology 607
    - Diagnosis 611
    - Complications, Sequelæ and Associated Diseases 615
    - Clinical Varieties 616
    - Treatment 618
    - Prognosis 619
    - Pathology 620
  - Acromegaly 623
    - Etiology 623
    - Symptomatology 623
    - Diagnosis 631
    - Complications, Sequelæ and Associated Diseases 635
    - Clinical Varieties 635
    - Treatment 637
    - Prognosis 638
    - Pathology 638
  - Pituitary Polyuria 641
    - Etiology 641
    - Symptomatology 642

PAGE
Diagnosis 645
Complications, Sequelæ, and Associated Diseases 648
Clinical Varieties 648
Treatment 649
Prognosis 653
Pathology 653
Pituitary Glycosuria 659
Pathogenesis 659
Symptomatology 660
Diagnosis 663
Complications, Sequelæ, and Associated Diseases . . . 664
Clinical Varieties 664
Treatment 666
Prognosis 666
Pre-Adolescent Bilobar Variety 667
Symptomatology 667
Diagnosis 673
Acromegaly, Polyuria, and Glycosuria 675
Etiology 675
Symptomatology 675
Diagnosis 684
Complications and Sequelæ 691
Associated Diseases 691
Clinical Varieties 692
Treatment 693
Pathology 693

LIST OF ILLUSTRATIONS

VOLUME VIII

SECTION XI: DISEASES DUE TO INTOXICATIONS

CHAPTER VII

MILK-SICKNESS

FIGURE PAGE
1. Eupatorium ageratoides 124

SECTION XII: DISEASES OF THE ENDOCRINE GLANDS

CHAPTER IV

GAUCHER'S DISEASE

1. Section of spleen, low power, showing dilated venous sinuses lined by large cells and distended by red blood-cells 320
2. Section of spleen, high power, showing the character of the connective tissue septa between adjacent sinuses 321
3. Section of liver, low power, showing the increase in interlobular connective tissue, and invasion into the lobules 322
4. Section of liver, high power, showing relationship of large cells to connective tissue, also large cells situated in the sinusoids . . 323
5. Section of retroperitoneal lymph-node showing masses of large cells separated by areas of normal pulp-cells 326
6. Section of bone-marrow, most of the field being occupied by large cells somewhat compressed and elongated 327

CHAPTER V

DISORDERS OF THE PITUITARY GLAND

CASE FIGURE
I. 1. Note short stature, short long bones, virgin mammæ, absence of axillary hair, and of girdle obesity . . 349
2. Posterior view of same case 349
3. Note practically normally-sized sella turcica 351
4. Note small hand, fragile metacarpal and phalangeal bones 352
5. Twelve months old hypophysectomized dog, and control of same litter 368

III. 1. Note short stature, small hands, fragile bones, and slight suggestion of girdle and upper thigh obesity . . . 387
2. Posterior view of same case 387

CASE	FIGURE		PAGE
	3.	Note character of hands and girdle obesity	388
	4.	Note small hand, broad palm, and short fingers	389
	5.	Palmar view. Note broad hand and short fingers	390
	6.	Roentgenogram of head, showing small sella turcica	391
IV.	1.	Note absence of marked osseous underdevelopment	397
	2.	Note different character as compared with pre-adolescent anterior lobe hypoactivity	398
	3.	Posterior view. Note absence of girdle obesity	399
	4.	Note small sella turcica	401
	5.	Note hands, more characteristic of gonad deficiency, and very slight fullness about thighs and abdomen	402
V.	1.	Note extreme height, and unusual length of long bones	406
	2.	Note length of long bones and long, tapering fingers	407
	3.	Note marked enlargement of sella turcica	410
	4.	"Showing patient's emaciation and infantilism"	411
	5.	"Pituitary in a man of forty"	414
VI.	1.	Note well-developed long bones, absence of adiposity, and of girdle obesity	426
	2.	Roentgenogram of head, showing large sella turcica	427
	3.	Perimeter chart. Bilateral homonymous hemianopsia	429
	4.	One year following operation. Note normally sized hands	430
	5.	Roentgenogram of head one year following operation	432
VII.	1.	Patient at ages of six and twelve. Note beginning obesity	447
	2.	Patient aged fifteen, anterior view	448
	3.	Posterior and lateral views, showing broad pelvis and enormous girdle obesity	449
	4.	Note dedentition	450
	5.	Note tapering fingers, abdominal and mons pads, and tiny genitalia	451
	6.	Note classical hands, narrow dorsa, free from fat pads, tapering terminal phalanges, and small nails	452
	7.	Note long, fragile metacarpals and phalanges, and tapering unguinal phalanges	453
	8.	Roentgenogram of skull	454
	9.	Normal perimeter chart	455
	10.	Comparison of Case VIII, pre-adolescent bilobar hypopituitarism, with Case V, pre-adolescent posterior lobe insufficiency	464
VIII.	1.	Note marked obesity of girdle type	472
	2.	Posterior view of same patient	473
	3.	Note small hands, tapering fingers, youthful face, and small canines	474
	4.	Lateral view, showing girdle obesity	475
	5.	Note marked tapering of fingers, delicate nails, etc.	476
	6.	Roentgenogram of head, showing small sella turcica	478
	7.	Note marked chloasma pigmentation about neck and upper chest	480
	8.	Note small hand, tapering fingers, chloasma, and vitiligo	481
IX.	1.	Note classical girdle and upper thigh obesity	487
	2.	Anterior view of same patient	487
	3.	Lateral view of same patient	488
	4.	Roentgenogram of head, showing small sella turcica	490

CASE	FIGURE		PAGE
X.	1.	Note small stature, osseous underdevelopment, girdle obesity, and small hands and feet	499
	2.	Lateral view of same patient	499
	3.	Posterior view, accentuating girdle obesity	501
	4.	Note girlish type of face, short, tapering fingers, etc.	502
	5.	Roentgenogram of head, showing small sella turcica	503
	6.	Note long, slender, metacarpal and phalangeal bones	505
XIII.	1.	Comparison of Cases X and XIII, anterior view	515
	2.	Comparison of Cases X and XIII, lateral view	516
	3.	Comparison of Cases X and XIII, posterior view	517
XIV.	1.	Note good osseous development, denoting normal pre-adolescent anterior lobe activity. Obesity of girdle type	525
	2.	Lateral view, showing girdle obesity, prominence of lower abdomen, obesity of upper thighs, comparative slenderness of lower legs, and absence of cuffing about wrists and ankles	525
	3.	Note marked separation of upper central incisors	526
	4.	Roentgenogram of head, showing small sella turcica	527
XV.	1.	Note slender, gracile type of make-up, preceding onset of pituitary deficiency	530
	2.	Same case after onset of obesity	532
	3.	Note characteristic girdle obesity	532
	4.	Perimeter chart. Note very slight contraction of visual field	534
	5A. & 5B.	(Cases I and XIV). Comparison of osseous development of pre-adolescent and postadolescent anterior lobe hypoactivity	540
XVII.	1.	Roentgenogram of head. Note very small sella turcica, with partial approximation of anterior and posterior clinoid processes	555
XVIII.	1.	Roentgenogram of head, showing normal sella turcica	559
XX.	1.	Roentgenogram of head, showing normal sella turcica	566
XXII.	1.	Roentgenogram of head, showing small sella turcica	573
	2.	Graphic chart of pulse-rate before and after administration of atropin sulphate, 1/30 grain	574
XXIII.	1A.	Note large stature, enormous obesity, particularly about hypogastrium and mons, somnolent expression, and drooping head	589
	1B.	(After treatment). Note decided decrease in obesity, particularly about abdomen and mons, decreased somnolence, increased alertness of expression, erect bearing, etc.	589
	2.	Note spade-like hand, broad palm and wrist, short and stubby fingers, with tendency to blunting, mammary development, and hirsuties	590
	3.	Note short, broad teeth, with good alignment and occlusion, and absence of separation	591
	4.	Roentgenogram of head, showing small sella turcica	594
	5A.	Note marked obesity about hypogastrium and mons, mammary development, spade-like hands, and stupid, apathetic expression	597

CASE	FIGURE	PAGE
	5B. Same case after treatment. Note marked decrease in obesity, loss of apathy, and increase in alertness and erectness of position	597
	6A. Posterior view. Note obesity and posture	599
	6B. Note decrease in obesity and change in posture after treatment	599
XXIV.	1. Note remarkable height as compared with normally sized male of corresponding age, extreme length of long bones, large hands, with long fingers and absence of spade-like character, and atypical distribution of pubic hair	608
	2. Note large, well-formed head, prominence of bony markings, and pituitary type of nose and chin	609
	3. Posterior view as compared with normal, showing striking increase in length of long bones	610
XXV.	1. Note short, heavy stature, with good muscular development, without obesity, broadness of hands, and prominence of jaw	625
	2. Note short hand, broad wrist and palm, and short fingers, with blunting	627
	3. Roentgenogram of normal sella turcica, showing no excavation or erosion	628
	4A. Note broadening and shortening of metacarpals and phalanges, with definite mushrooming of unguinal phalanges	629
	4B. Comparative study of hand of bilobar hypopituitarism	629
XXVI.	1. Note eunuchoid type, with overdevelopment of long bones; long hands, with slender, tapering fingers	642
	2. Graphic chart showing amount of specific gravity of urine voided, and influence of Pituitrin and Pituitary Liquid	644
XXVII.	1. Urine chart of case of pituitary glycosuria	665
XXVIII.	1A. Note short, stocky make-up, with unusual muscular development, square head, prominence of features, and absence of adiposity	668
	1B. Note mandibular prominence	668
	2. Note broadness of face, prominence of bony parts, large teeth, and separation of upper central incisors	669
	3. Note musculature and short, broad character of hands, with very short nails, short fingers, and broad wrists	670
	4. Sella turcica not well defined	672
XXIX.	1. Note acromegalic stature, muscular development, long torso as compared with extremities, large, spade-like hands, and abnormal distribution of abdominal hirsuties	679
	2. Posterior view showing character of hands, musculature, and disproportion in measurements	679
	3. Lateral view of same patient	680
	4. Note broad face, short, broad teeth, crumbling and separation of upper central incisors	681
	5. Note spade-like hand, broad wrist and palm, short, stubby fingers	682
	6. Normal sella turcica, measuring 10 x 16 mm.	683
	7. Broad, spade-like hand, dense and thickened metacarpal and phalangeal bones, with mushrooming of unguinal phalanges	684

List of Tables

TABLE PAGE
1. Classification of disorders of the pituitary gland . . 342
2. Hormonic signs of the anterior lobe of the hypophysis . 354
3. Hormonic signs of the posterior lobe of the hypophysis . 413
4. Hypopituitarism 440
5. Subsequent course and therapy (of Case XXIII) . . 598
6. Anterior lobe hyperpituitarism 614
7. Gradwohl's estimations of glycosuria and glycemia . . 677

PRACTICE OF MEDICINE

VOLUME VIII

SECTION XI

DISEASES DUE TO INTOXICATIONS

CHAPTER I

ALCOHOLISM

By Stephen Perham Jewett, M.D.

General consideration, p. 1—Causes for excessive drinking, p. 4:—Personal condition, p. 4; Social conditions, p. 4—Physiological effects of alcohol, p. 5—Pathological changes due to alcohol, p. 5—Forms of alcoholism, p. 6:—Acute alcoholic intoxication, p. 6; Chronic alcoholic poisoning, p. 6—Characteristic clinical forms of alcoholism, p. 9:—Pathological intoxication, p. 9; Delirium tremens, p. 9; Acute hallucinosis, p. 12; Acute paranoid form, p. 13; Chronic paranoid form, p. 13; Korsakow's disease, p. 14; Alcoholic deterioration or dementia, p. 14—Other less characteristic types, p. 15:—Pseudoparesis, p. 15; Alcoholic epilepsy, p. 15; Alcoholic polyneuritis, p. 15; Pseudotabes, p. 16; Alcoholic "wet brain" or alcoholic "meningitis," p. 16.

General Consideration.—Various meanings have been given by different writers to the term ''alcoholism.'' Hence, the viewpoints from which the subject may be discussed are numerous. The limits of this work will permit scarcely more than a very brief mention of some of the more important medical phases of the topic. The multiplicity of causes for drinking to excess, psychological and otherwise, and the many sociological aspects of the subject must be dealt with even more briefly.

Of all the pharmacotoxins with which pathology and particularly neuropathology are concerned, none is so important as ethyl alcohol. In spite of this fact, however, it is a dangerous poison to but a small percentage of those who use it. In this country, at least, it is chiefly whiskey-drinking which is responsible for the greater portion of chronic alcoholism. Beer and ale, particularly in those of sedentary habits, also enter into its pathological effects. Wine, with the exception of champagne, is a small factor in its pathology, at least in the United States.

It is a peculiar fact that those countries in which the consumption of alcohol seems to be most universal are the very ones which are in the vanguard of civilization. This is not only true to-day, but has been in the past, and those very periods in which alcoholic indulgence was most rife in the history of certain nations, were in many respects the most brilliant chapters of their national life. All the strongest and most dominant races, throughout the historic periods, have displayed a strong craving for the stimulation afforded by alcohol. Indeed, alcohol has been so intimately associated with the development of mankind, that one wonders just what present day civilization would be had alcohol never been discovered. In the past also alcohol has performed a great work as an eliminator of the weak and unfit. It was this particular class which was killed by its abuse, while those of greater strength were left to profit by its use under certain conditions.

Much has been said and written of the bad effect of chronic alcoholism upon heredity. The underlying condition of a degenerative nature, upon which alcoholism has developed, will be found to be the really determining factor in the greatest number of cases. In the author's experience, alcoholism occurs in not more than 4½ per cent. of the ascendants of the insane and mental defectives.

The susceptibility to alcohol varies greatly in different individuals and in different races. Why is it, for instance, that one man, who has been a daily consumer of alcohol for many years, reaches a ripe old age and succumbs with mentality unimpaired, and with no inflammatory or degenerative changes due to the use of alcohol, while another, in early adult life, suffers in one organ or other, after a comparatively short use of the same intoxicant? Similar questions may of course be asked concerning many other poisons. Why, for example, do only about 3 per cent. of syphilitics finally end as paretics? The answer is undoubtedly the same in all cases. It is because of the original inferiority of an organ, which in some instances is the central nervous system, and in others the vascular system, the kidneys, liver, etc.

In his "Study of Organ Inferiority and Its Psychological Compensation," Adler states: "A certain probability, which is in accord with biological conditions, would have it appear that, fundamentally, just the most highly differentiated cells and cell-complexes have come out the worst, while the tissues, of lesser capacity, which owe their development to an earlier embryologic epoch, may be normally or even supernormally developed. . . . The normal structure, and wear and tear of the organ, give place to regressive phenomena, which are just as much determined in their nature by the morphologic inferiority of the organ, as by the special causes setting the disease in action.

"Organic nerve diseases, however, are, according to our premises, only special cases in which the localized inferiority is inclined to inflammatory or degenerative transformation."

It would seem that this offers the best conception of the determining causes under consideration. It explains why alcohol, even in small doses, is death to some, while others are able to tolerate large and continuous doses for years. It also shows why one man at 30 may suffer from the effects of a cirrhotic liver, while another, at the same period, breaks down with an alcoholic psychosis.

In other words, alcoholism is very often but the expression of a weak and unstable nervous system, rather than the sole cause of the same. Indeed, those radical reformers who view the subject only from their standpoint are as much in the wrong as the selfish and sordid liquor interests which would reap profit from a degenerate, drunken creature. In spite of the great misuse of alcohol by some persons, and its degenerating effects upon certain constitutions, the author is convinced that it has its right place in the world, not only from a purely medical, but also from a sociological viewpoint. The very type of individual who misuses and abuses it will always find a substitute when alcohol cannot be obtained, for the energy of their mental complexes is bound to find an outlet along some channels.

Insanity and disease will continue to flourish, even if laws prohibiting the manufacture and sale of alcoholic beverages are made and drastically executed. The prohibitionist will still find State Hospitals for the Insane, as well as poorhouses and cemeteries, and he will also find them still pretty well filled. In the very states of the Union where the prohibitory laws have been longest effective—Maine and Kansas—insanity continues to increase. And in New York during the past three years, in spite of a great diminution in the admission of chronic alcoholics to the hospitals, the insane continue in increasing numbers to fill the state institutions. Crime and poverty will no doubt be diminished by prohibition, but perhaps not more than by some measures of control.

It simply means from a medicopsychological standpoint, that the person who is unable to make an adequate adjustment to the ordinary events of life as they roll before him will be unable to do so either with or without alcohol. Inebriety is but one of the many forms of symptom-behavior which are common in degenerate types. Alcohol may be the precipitating factor causing the final break, but the real underlying cause is the general organic weakness in the individual, plus the determiners or lack of determiners received from the germ-plasm of his ancestors.

What is greatly to be desired is some drastic method of control. More would be gained for the cause of civilization and for true temperance by such measures than by any prohibitory laws that may be adopted. What has been accomplished by the Liquor Control Board in England is well worthy of study by those who really desire to gain results in this great problem. Under its direction and supervision, drunkenness and the evils arising from the misuse of alcohol generally have been cut down more than one-half since 1915, when the Board went into operation. Prior to that time, the curse of alcoholism in England was described as a greater menace than the German submarine, and this no doubt was true. In some districts they closed some of the public houses and many of the breweries. They turned out, in many cases, the proprietors and managers, whose sole aim seemed to be to make profit from the sale of drink. They took over the management of these places and encouraged the sale of food rather than of drink. The hours of opening were restricted to mealtimes, and minors were not permitted to drink. Saturday closing was enforced. Many other changes were instituted which have worked for the betterment of the working people in particular. If in our own cities and towns the local Boards of Health could exercise a similar authority, or special boards for certain districts could be established, it would be a long step in the right direction.

Causes for Excessive Drinking.—PERSONAL CONDITION.—There are, of course, large numbers of persons whose heredity is of the best, and who show no defects of intelligence or of emotional or volitional life, but who help swell the ranks of the chronic alcoholics, finally becoming deteriorated both mentally and physically. Many a man of this type drinks because *he has no other definite interests in life.* Drinking appears to be his one great hobby. However, it is now a much less popular form of diversion among this class than formerly. Such cases sometimes become total abstainers, following marriage and the acquisition of a family; others become reformed through religion, and still others through other interests of one kind or another. Much can be done for persons of this class, if mental deterioration has not set in.

We have again those cases in which excessive drinking and drunkenness are but the *expression of a psychosis.* The general paralytic who suddenly changes from a total abstainer or very moderate drinker to an inebriate of the worst type is a case in point. The schizophrenic is another, and the early manifestations of his disease are often so mixed up with the picture of an alcoholic psychosis, that one is very likely to confound the two. The cyclothymic, who starts to drink during a depression, as a means of ridding himself of a feeling of inadequacy and restlessness from which he suffers on such occasions, is not at all uncommon. Under the influence of the alcohol, a state of excitement sets in, which causes him to indulge even more freely, till the attack passes away. There are many of this class, too, who only drink during the exalted phase of their disorder. Then they become convivial and so filled with the joy of living that they seek gay company and frequent places they never dreamed of entering during the intervals between these attacks. It is the above type which help to increase the number of *dipsomaniacs* or periodical drinkers.

The periodicity which characterizes the drinking of the dipsomaniac is often only the expression of an underlying epileptic personality. Here the ordinary convulsive seizure or fainting attack is replaced by an intense state of excitement, which seems to be initiated by the alcoholic indulgence. There seems to be a periodic craving for a state of unconsciousness in some of these epileptic characters, and when this desire comes they will drink till a state of coma ensues, and then appear satisfied. Between the paroxysms they become total abstainers.

The *neurasthenics and psychasthenics* are another class who often drink to excess through their inability to settle their complexes normally.

The constitutionally inferior and unstable individuals are generally prone to ride over each new painful situation in life by indulgence in alcohol or drugs. Such individuals are not able to transform lower enthusiasms into higher ones and thus always live on a low plane.

SOCIAL CONDITIONS.—In general, bad social conditions, with too long hours of work leading to fatigue, insufficient healthful recreations, too little and badly prepared food, irregularity in eating, etc., all help to prepare the soil for inebriety.

Whatever helps to breed crime also aids in producing alcoholism, and not the least of these is idleness. This latter, with the lack of some healthful interest or hobby, is bad enough in any person, but in the unstable it becomes disastrous. During the period of the war, when it was a violation of the statutes not to be regularly employed, the admission of cases to the alcoholic wards of Bellevue Hospital was reduced two-thirds. Unscrupulous liquor dealers and bartenders, who break the laws, sell to drunken men and minors, and who permit all night and Sunday openings, are at the bottom of much of the mischief. The mere abolition of the saloon in itself will never suppress the habit of drinking. Filled with evils as it has been in the past, something must be substituted for it, as it has had a very important place in the social life of the lower classes.

Physiological Effects of Alcohol.—Even at the present time, there appears to be some diversity of opinion as to the immediate effect of small doses of alcohol upon the human organism. Some maintain that it is a stimulant to the nervous system as well as to the heart and respiration. Others as insistently claim that it is a depressant and paralyzant from the first. We all know, however, that the pulse is increased in frequency and that the superficial vessels become dilated; it is because of this action that alcohol becomes so useful after long exposure to cold, when the blood has been driven from the skin, and the internal organs are in a state of congestion. It is for this reason, too, that bad results follow its use during continued exposure, as the bodily temperature really becomes greatly lowered.

It is quite doubtful whether it ever acts as a direct stimulant to the nervous system. The sense of rest and stimulation obtained during fatigue from small doses of alcohol is undoubtedly brought about by its paralyzing effects upon the sense-organs which convey the feeling and impression of fatigue. And its apparent stimulating effect upon the higher psychic powers is rather due to its paralyzing effects upon the inhibitory mechanism.

Small doses of alcohol increase digestive function by stimulating the flow of gastric juice. Larger doses retard this function, and in sufficient doses, stop it entirely. There is also a difference of opinion as to the food value of alcohol. Inasmuch as it readily undergoes decomposition into carbon dioxid and water, it is quite possible that it does diminish to some extent the consumption of the constituents of the body.

That it is a strong dehydrative agent, none can deny. Water is removed from healthy protoplasm, and for this reason, if taken in sufficient quantities and for a long enough period, it is bound to show its degenerative effects upon the tissues. And it is upon the tissue of the nervous system that it exerts its profoundest influence.

Pathological Changes Due to Alcohol.—These, in general, are arteriosclerosis, cirrhosis of the liver, fatty heart, congestion of the stomach with altered gastric secretion, and inflammatory conditions of the kidneys. In the central nervous system, destruction of the ganglion-cells takes place; there are neuritic processes in the peripheral and optic nerves and in the central nervous system, as well as degenerative changes in the fibers and cells, and an increase in the supporting tissues, due to changes in the blood-vessels. Pachymeningitis, edema, congestion, thickening and opacity of the pia-arachnoid, or sometimes punctate hemorrhages into the brain are found. These changes vary in degree and kind with the individual susceptibility of the tissues and organs to the intoxicant. No doubt many of these are brought about in an indirect way through metabolic disturbance, rather than by the direct action of the alcohol itself.

FORMS OF ALCOHOLISM

Acute Alcoholic Intoxication.—SYMPTOMATOLOGY.—Here the symptoms are chiefly referable to the nervous system. There is a decrease in the clearness of sensory perception, judgment and thought are impaired, and the finer emotions are dulled. Following a brief excitation, there soon follows inhibition and disturbance in coördination of movements. Consciousness becomes dimmed, then lost, and finally sensory and motor paralysis ensue. In extreme cases the stupor becomes profound, the temperature subnormal, and collapse and even death may result.

DIAGNOSIS.—Mistakes in diagnosis are very often made in the extreme states of intoxication just mentioned. The diagnosis should never be made from the odor of alcohol on the breath, and the comatose state alone. A careful physical examination may save later embarrassment and much injustice to the patient, and sometimes even his life.

TREATMENT.—Most cases of this nature require merely **sleep** and **removal of the intoxicant.** In certain states of excitement and in the extreme cases, when collapse threatens, something more is needed. In the former, a **hypodermic of apomorphia** will secure emesis and later give the required rest. In the latter it may be necessary to **wash out the stomach,** apply **heat** to the extremities and administer cardiac stimulants such as **adrenalin chlorid, camphor-ether,** etc., or **black coffee.**

Chronic Alcoholic Poisoning.—SYMPTOMATOLOGY.—The phenomena of chronic alcoholic poisoning are extensive and characteristic. Perhaps the most typical symptom is a tremor. This is seen in the peribuccal muscles, the tongue and hands. Other muscles are also affected, but not so typically. Its rhythm is regular and constant, and the oscillations rather slow. In pronounced cases it may be so marked as to interfere with the patient's ability to raise a glass of water to his lips, but on the other hand, it may be so slight as to be noticed only by having him stretch and extend his fingers. If one places the tips of the patient's fingers perpendicularly on the palm of one's hands, a peculiar grating sensation may be experienced. It is unusually aggravated in the morning. Food and drink tend to reduce it temporarily.

Changes in the liver (cirrhosis), in the heart and blood-vessels, in the kidneys, pancreas, etc., with all their attendant symptoms, are common. The skin becomes red and bloated, and acne rosacea and venectasias are seen. Catarrhal conditions of the larynx, pharynx and stomach occur. Gastritis may be particularly troublesome.

Sensibility to pain becomes heightened. Painful pressure points are found in various places—over the nerve trunks, over the front of the thighs, and in the calves of the legs. Neuralgias, sciatica and lumbago often occur. The tendon reflexes may be increased or diminished, but in uncomplicated cases are usually not changed.

The mentality undergoes a weakening which usually affects the highest attributes of the mind. The powers of discrimination become impaired, and as long as the system is under the influence of the poison, the inebriate will lay the blame for his drinking upon anybody or anything but himself. A quarrelsome, jealous disposition results and his capacity for work becomes greatly reduced. The will becomes gradually more and more weakened and deterioration may become extreme.

Upon this basis, any of the characteristic alcoholic psychoses may develop.

TREATMENT.—It is very doubtful whether cases of chronic alcoholism can be successfully treated without **isolation,** at least for a certain period. The temptation to drink is so very firmly implanted, that nothing permanent may be expected in the majority of cases, except from institutional treatment. Brief periods of treatment usually yield very unsatisfactory results. At least six months is required and often a year or two may be necessary.

The patient should be studied from every angle. Not only his physical condition, but his entire personality needs to be closely scrutinized. Often some underlying mental or nervous condition may be discovered which leads to periodic drinking. This is particularly true of the cyclothymic constitution. Here the patient may be educated to seek professional advice when he feels an attack coming on and in this way measures may be adopted in many cases to prevent the alcoholic debauch which would otherwise follow.

The *medical treatment* follows general lines. Any underlying **physical cause** for the disorder should, of course, be **removed** if possible. Every method should be employed to bring the health of the patient to a normal state. *Nothing is to be gained by gradually* **withholding the alcohol.** The sooner it is done, the better for the patient. Three or four days may be required in most cases, but it may take longer. During this period, it is necessary to resort to some sedative in order to "hold" the patient. The extreme to which this expedient has to be executed varies with the individual, and especially with his legal status in the institution if he is to be in one. Voluntary institutional patients will, as a rule, stand but little suffering and many almost no discomfort. Indeed, in a few cases some sedative has to be pushed to great extremes.

The average case may be treated during this period about as follows: Place the patient in bed and administer a dose of **calomel and soda.**

Order a cleansing **enema,** and if possible a **high colonic irrigation.** Repeat the latter twice daily for three days. Give the following medication:

℞

Tincturæ nucis vomicæ	ʒvi	(22.5 c.c.)
Tincturæ capsici	ʒij	(7.5 c.c.)
Ammonii bromidi	ʒviii	(31.1 grams)
Elixir ammonii valerianati	℥ij	(59.2 c.c.)
Syrupi zingiberis	℥ij	(59.2 c.c.)
Aq. destillatæ q.s. ad	℥viii	(236 c.c.)

M. Sig.: One teaspoonful every two hours, slightly diluted. May be taken every three hours and then every four hours as the restlessness and nervousness decrease.

The first night or two, paraldehyd 2 drams to ½ ounce (7.5 to 15.0 c.c.) in a little sherry wine may be required for the sleeplessness. After this, 15 grains (0.972 gram) each of trional and sulphonal in hot milk are given for a few nights, and finally the hot drink of milk, minus the drugs. Dispense with all drugs as soon as possible.

The **diet** for the first day or so should consist of broths, milk, etc. Gastric irritation is sometimes very obstinate and the patient is able to retain but little. Hot clam bouillon can often be retained when nothing else can. As the appetite improves, the nourishment should of course increase. The aim should be to inculcate a taste for plain and wholesome food. Condiments should be used very sparingly. The use of sugar is to be encouraged after the acute symptoms have subsided, and this can often be given in the form of confectionery. Water should be drunk in plenty and with regularity.

After the third or fourth day, the patient is, as a rule, able to be up. A definite program should be made out for the day so that no time whatever is left unoccupied. **Hydrotherapy, massage, psychotherapy, outdoor exercise, games,** etc., should all be used.

Many "specifics" have been extolled for the cure of alcoholism. They are in no sense true specifics, however. Without conscientious desire to remain away from drink, and a consequent full coöperation on the part of the patients, nothing permanent can be expected in any case. There can be no halfway measures. They must be taught that for them, temperance must mean total abstinence. One drink, as a rule, and they are lost.

In New York and some other states, provision is made in the statutes for the legal commitment of inebriates. This step is necessary in many cases.

PROGNOSIS.—This, in a very large measure, depends upon the basis on which the disease originally developed. Hopes for permanent cures are scarcely to be expected in the large numbers of mentally deficient individuals, affective deviates and other abnormal types. Once the habit is firmly established in this class, nothing short of permanent institutional life is likely to stop it.

On the other hand, in those individuals with a normal make-up, much may be expected if the disease has not advanced too far. It is quite possible to obtain permanent results in one-half or even more of the cases of this sort.

Certain of the dipsomanic cases offer fair chance for cure. In these deterioration is less likely to set in because of the brief duration of the attacks. Here, if one is able to make a proper diagnosis of the underlying condition, the patient may be brought to a proper understanding of his case and be taught how to avoid his alcoholic habits.

In any event, the outlook depends upon the patient's own desire to be cured. Recovery cannot be forced upon any of them and there is no specific for the disease.

CHARACTERISTIC CLINICAL FORMS OF ALCOHOLISM

The mental and nervous disorders for which alcohol is at least the precipitive cause will now be briefly considered. The mental disorders (alcoholic psychoses) will be taken up under the following headings:

(*a*) Pathological intoxication.
(*b*) Delirium tremens.
(*c*) Acute hallucinosis.
(*d*) Acute paranoid form.
(*e*) Chronic paranoid form.
(*f*) Korsakow's disease.
(*g*) Alcoholic deterioration.
(*h*) Less characteristic types.

Pathological Intoxication.—The symptoms of this disorder differ considerably from simple intoxication or drunkenness. It follows immediately after the consumption of even a small amount of alcohol in certain individuals of peculiarly predisposed make-up. Such a person may at once become noisy, loquacious and elated, or quarrelsome, boisterous and pugnacious. Such symptoms may last from a few to several hours. On the other hand, such a person might become morbidly depressed and even suicidal. Even a profound state of coma may ensue upon the imbibition of what would scarcely affect the normal individual. Persecutory delusions, and auditory as well as visual hallucinations may occupy the field for a brief time. Very often the symptom-behavior becomes of such a character that isolation in the psychopathic ward of a hospital becomes necessary; in a few hours the subject is quite normal and ready for discharge. Other persons of a psychoneurotic make-up may exhibit pronounced hysterical attacks after indulging in small amounts. Needless to say, such types as the above should studiously avoid alcohol. The treatment of this condition, once developed, consists merely in removing the intoxicant and temporarily isolating the patient so that no harm may come to him through his antisocial conduct.

Delirium Tremens.—ETIOLOGY.—Because of the rather high mortality resulting from this disease, it is highly important to the medical practitioner. The condition usually develops in certain chronic alcoholics following a particularly hard debauch, and especially in those who are liable to mental or sensory hyperesthesia. It is also likely to follow a severe or even slight trauma in the same class of individuals. Although abstinence in chronic drinkers is often given by the patients themselves as a cause for the malady, it is very doubtful if any case is due to the above. Among many hundreds of cases personally investigated by the author, there was never one found in which this could absolutely be proven as the only etiological factor.

In this disorder there is a toxic interference with the receipt of sensory stimuli, and through the vegetative nervous system an increased reaction to emotional stimuli.

SYMPTOMATOLOGY.—The symptomatology is fairly uniform, although subject to some variations. In typical cases the patient is bathed in perspiration and the skin is cool and clammy. The eyes are often bloodshot. There is a rapid pulse with low tension, and in uncomplicated cases the temperature is normal or but slightly elevated. An occasional case will run its entire course with a high fever, even in the absence of any physical signs of an infection.

Coarse tremors are the rule, and these may affect the entire musculature. On the other hand, only the peribuccal muscles, tongue and fingers may be involved.

Clouding of the sensorium, with absence of lucidity, is characteristic. False sense-perceptions of the visual type predominate. All sorts of loathsome creatures may be seen; spots and shadows are mistaken for animals, and the patient may be seen busily engaged in taking insects from the bedclothes or in driving animals from his bed. Auditory hallucinations usually accompany the visual, and the patient may be in a state of apprehensive terror. Some one is going to shoot him, electrocute him or cut him to pieces. Voices are constantly heard telling him this. Often the victim is busy with his daily occupation. The author has often had half a dozen drivers at one time who thought themselves actually engaged in their work. Their cries and orders to their horses could be heard all over the ward.

Occasionally, instead of the extreme apprehension and restlessness, one meets with the opposite mood. The patient appears to be intensely interested and amused by his experiences. One patient was being covered with horse manure and was in a state of glee and laughter; another was being entertained by a duck walking along the wall.

All sorts of amusing incidents are related. These cases usually offer a more hopeful outlook, as the patients are not so likely to wear themselves out with excitement.

CLINICAL VARIETIES.—Certain abortive types are common. The sweating, tremors, apprehension and sleeplessness are present, but hallucinations are absent and the sensorium is quite clear. Such cases run a brief course and there is almost no mortality. These are the cases of *delirium sine delirio* and should not be properly classed as delirium tremens.

There are two types of delirium tremens, the sthenic and the asthenic. In the former, the delirium develops rapidly and reaches an extreme state of intensity. These cases run three or four days and terminate in recovery, following a prolonged sleep, or die of exhaustion, acute dilatation of the heart, etc. This type is characterized by a hyperemia of the brain. About 85 per cent. of all the cases observed by the author have been of this type.

In the asthenic type, the delirium is of a lower grade. It is several days in reaching its height and runs a more protracted course. The brain is anemic in this class of cases. About 15 per cent. of all cases comprise this group. Pneumonia is a frequent complication in this type.

The mortality in untreated or improperly treated cases runs from 25 per cent. to 40 per cent. In properly managed cases, it is about 20 per cent. or less.

TREATMENT.—The chief indications in treatment are: (1) elimination of toxic products from the system; (2) support of the vital functions; (3) control of the delirium.

In executing the above indications, it is well to bear in mind the two types of cases described—the sthenic and the asthenic—inasmuch as the treatment for one differs considerably from the treatment of the other.

In the sthenic cases, as soon as possible after the case comes under observation, meet the first indication as follows: Administer grains iii-v (0.195-0.324 gram) of **calomel** and order high colonic **irrigations** of **normal saline solutions.** After thorough cleansing of the lower bowel, fill the colon with this solution and repeat as often as once every two hours for the first few hours. Resort to **hypodermoclysis** or even **intravenous injections** in very severe cases. This dilutes the toxins and affords an ample supply of fluids for the circulatory system, which in this type of cases is considerably diminished. The pulse will become less rapid under these measures, and free actions of the kidneys will take place.

As soon as the volume of blood has been increased by the above methods, **larger doses of saline cathartics** should be given. Continue to keep up the volume of blood by giving large quantities of water by mouth, as the bowels can no longer be used for the purpose of absorbing fluids because they are now being used as eliminative organs. Repeat the salts until large watery evacuations occur.

The second indication is best met by administering as much **nourishment** in the form of **liquids** as can be retained. In those cases in which the heart action is poor, inject **spartein sulphate** in 2 grain (0.13 gram) doses every three hours. This not only helps support the heart, but acts also as a diuretic. If collapse supervenes, it is best met by the injection of **adrenalin chlorid,** 15 minims (0.92 c.c.) into a muscle, or 5 minims (0.3 c.c.) into a vein. Follow this immediately with **camphor in oil,** 5 grains (0.324 gram) into a muscle. The digitalis group may now be introduced by injecting 1/50-1/90 grain (0.0013-0.00072 gram) of **strophanthin** into a muscle. At the same time give 30 minims (1.9 c.c.) of a good **digitalis preparation** by mouth and repeat every 4 hours for three or four days. This is introduced by the strophanthin, as it requires about 36 hours for the digitalis to act when taken by mouth.

The administration of the saline solution, and the regular injections of spartein, as mentioned, will usually obviate the necessity of having to resort to the other measures mentioned under the second indication.

The control of the delirium, or the third indication for treatment, should **not** be met by administering sedatives such as **morphin, bromids, chloral, hyoscin,** etc. The death-rate will be greatly increased by such drugs. Since the author has abandoned these drugs in such cases, the mortality has been decreased by one-half or more. In the sthenic cases now being considered, the drug, which has been found most useful in controlling the delirium, is **gelseminin.** This alkaloid should be injected subcutaneously every two hours in doses of 1/25 grain (0.00259 gram), repeating until full physiological effects are obtained. This drug has an action similar to opium, but does not tie up the secretions and excretions in the same manner. The hyperemia of the brain and the consequent cerebral excitement is greatly lessened. To supplant this drug, a prolonged **neutral bath** may be used, and usually gives good results.

In the asthenic cases, the same eliminative measures should be carried out. **Spartein** may also be safely used for the heart, and is best given as advised above. In the control of the delirium in these cases, however, the treatment differs. Here **gelseminin is contra-indicated** inasmuch as it still further lessens the blood supply of the brain, which is already too low. Give instead 1/30 to 1/15 grain (0.00216-0.00432 gram) of **strychnin sulphate** every four hours. This will increase the cerebral blood supply, and in these asthenic cases acts as a sedative and controls the delirium.

In all cases it is best to **withhold the alcohol rather rapidly.** This will result more favorably, in most cases, than withholding it abruptly. Reducing the accustomed daily dose by one-half is a good method. By these means all alcohol can be withheld in four or five days, as a rule.

Under the treatment outlined above, **sleep-producing drugs** are *rarely required.* The author once more wishes to warn against their abuse in delirium. **Thorough elimination** is the chief indication, and this in itself aids greatly in controlling the delirium, along with the other measures recommended. Frequent **lumbar puncture** has been used, but the author is not yet convinced of its efficacy.

PATHOLOGY.—The structural changes in the brain do not differ from those seen in chronic alcoholism, without delirium. They usually relate to ganglionic cells, which are found to be shrunken. Considerable gliosis, with vascular proliferation and round-celled infiltration, is the rule. Recent hemorrhages have been observed. The chief factor in the production of the delirium is a toxic one. This consists partly in the alcohol itself, and partly in the result of tissue disintegration and in fermentation products.

Acute Hallucinosis.—This condition develops in chronic alcoholics under much the same condition and circumstances as delirium tremens; it differs from the latter disorder in many important respects. Here the receipt of sensory stimuli is not interfered with, and instead of an increased reaction to emotional stimuli, there is a lack of the same. The sensorium remains unclouded and orientation is intact. Auditory hallucinations predominate instead of visual. Restlessness is absent and coarse tremors are not in evidence. Consistent delusions are present and the disease pursues a slower course than tremens. Indeed, some cases run a very protracted course and become chronic, as will be noted in another section.

The patient hears voices calling him all sorts of vile names. These are very often of a sexual nature. He is called a masturbator, onanist and other similar terms. Some one is going to electrocute him, shoot him or cut him into a thousand pieces. Others are told they are "no good," that "they had best shoot themselves or jump into the river." As their delusions harmonize with their hallucinations, they often execute these commands and attempt suicide or shoot their suspected persecutors.

Isolation is necessary, and, in many, commitment to an institution for the insane. Many recover as soon as the alcohol is removed for a few days. In some cases, in which there is but little mental deterioration, they quit their drink entirely following such an episode and never take to it again. Recurrences follow the same conditions which resulted in the first attack. Others have episodes following even a slight amount of drink.

Acute Paranoid Form.—These often develop out of the former state, or follow an attack of delirium tremens. A case in question will illustrate this disorder.

A patient of the chronic alcoholic type had been on a particularly hard spree. Hallucinations developed. He heard voices saying that he was a bad man, that he had had sexual relations with his neighbor's daughter. He was at loss to know who it was who accused him so wrongfully. Another neighbor quarreled with him, and because of this, he imagined it was this man who was spreading these terrible tales. He became quite depressed and went to the police and made a complaint about the party. The latter appeared and denied the story, and in turn accused the man of trying to blackmail him and of having struck him. It resulted in the poor victim's arrest and sentence to the workhouse for ten days. After having served his time, he bought a revolver and shot his suspected persecutor. His lawyer had him sent for observation, and then his sickness was discovered. After a few weeks away from drink his hallucinations left him and he gained insight into his delusional state and was discharged.

Chronic Paranoid Form.—This psychosis usually develops in a chronic alcoholic, and very often arises from the underlying jealous disposition so common in these types. He sees his wife talking to the grocer and imagines they are too friendly. The delusion soon develops that she is no longer faithful to him, so that, although she may be a woman of 50, he believes she is receiving all sorts of attention from different men. Suicidal and homicidal tendencies may develop. Considerable mental deterioration accompanies this form, and it is likely to become chronic. All sorts of ideas may be held by the patient—some one is using a dictagraph on him, electricity is applied by his enemies, etc.

The acute form usually requires hospital treatment for a longer or shorter time, while for the chronic type permanent isolation is usually necessary.

Korsakow's Disease.—This is a psychosis associated with a polyneuritis. The physical signs may be very extensive, including the typical foot and wrist-drop, or the evidence of the neuritis may be so slight that a search has to be made for it. The only manifestation may be a slight tenderness over the nerve-trunks of the lower extremities.

The mental symptoms consist of a peculiar disorder of the attention and memory, which results in defects in recording passing events. All sorts of fabrications fill in the gaps, and as the patient is composed and appears lucid, the casual observer might not detect the peculiar mental state. Such a patient, who perhaps has been in the hospital many days without being out of his bed, will tell in his calmest manner of his trips downtown and of his visits to his friends; he will tell of the various visitors who have been to call upon him, when as a matter of fact nobody has been to see him.

This disorder often develops after delirium tremens or merges into it from the latter. In fact, it is sometimes known as the *chronic alcoholic delirium.* A delirium is by no means necessary as a precursor of the condition.

A similar mental picture is often observed in other psychoses but may easily be differentiated from a true Korsakow by the history and physical signs in this syndrome. Some of the cases recover in a comparatively short time. Those developing after a delirium tremens are likely to run a long course.

This type is not likely to become dangerous and if conditions are proper may be cared for at home. Abstinence from alcohol and measures directed to restore the physical condition are the indications for treatment.

Alcoholic Deterioration or Dementia.—In this condition all the higher attributes of the mind first suffer. The patient loses his moral tone. His judgment becomes impaired and all sense of discrimination lost. He becomes careless and untidy in his habits and loses interest in everything but his desire to drink. He becomes irritable and quarrelsome, often commits antisocial acts and finally becomes a hopeless derelict. This condition may or may not be interrupted in its course by some of the above-mentioned disturbances.

The only treatment for this type is early isolation. If the symptoms are not too pronounced and the case is kept from alcohol for six months to a year, some improvement is likely to take place. If after one or two trials of this nature he resumes his former practice, the case is hopeless.

OTHER LESS CHARACTERISTIC TYPES

Among these may be mentioned alcoholic pseudoparesis and alcoholic epilepsy.

Pseudoparesis.—This type will show some or all of the pupillary disturbances found in general paresis and the changes in the knee-jerks found in that disorder. Grandiose delusions are present, and one is likely to think that one is dealing with a general paralytic of the expansive type. Examination of the spinal fluid will establish the diagnosis in these cases. In some cases the mental symptoms clear up rather rapidly following a period of abstinence.

Alcoholic Epilepsy.—Attacks of an epileptiform character take place in certain predisposed individuals, following even slight amounts of indulgence whereas, at other times, they are entirely free from the seizures. This form is particularly favored by some previous head injury.

A psychic equivalent may take the place of the regular convulsion in this form, and while in a confused and frenzied state the patient may commit acts of great violence and brutality. Following such an attack there is often an amnesia for the whole episode. Such cases assume great medicolegal interest and the author has seen a number of subjects who have committed murder and dreadful assaults.

The more purely neurological disorders due to alcohol will now be briefly discussed. Of greatest importance is:

Alcoholic Polyneuritis.—Probably two-thirds of all cases of polyneuritis are due to chronic alcoholism.

The lower extremities are first involved in the vast majority of cases, the peroneal nerves being chiefly affected. Often the disorder is first observed on one side, but it soon becomes bilateral. The tibial nerves next to the peroneal are, as a rule, affected. The nerves of the thigh and pelvis, and together with them, or often before, the musculospiral, and then the median and ulnar are involved.

In the severest cases, almost a complete paralysis occurs, and in such an event, even the musculature of the trunk, abdominal walls, etc., will be attacked.

In the very beginning of the disorder, a transient exaggeration of the reflexes may be noted. Almost always, however, the reflexes are very much diminished or even absent. Electrical stimulations will usually show R. D.

Foot and wrist-drop take place in the fully established cases. Before the former occurs, or after it has improved, and the patient is able to walk, the peculiar steppage or ''waddling'' jump is observed. Paresthesias, formication, etc., beginning in the feet, are often early symptoms. The motor disorders are the most characteristic features, although there are few cases in which sensory symptoms are entirely lacking.

Trophic disturbances often occur, the most important of which are hyperhidrosis or anhidrosis, and glossy or red skin. Considerable edema often occurs.

The mental disturbance known as Korsakow's psychosis, which sometimes accompanies this disease, has been mentioned.

Pseudotabes.—This is only a clinical form of polyneuritis found especially in alcoholics. It is peculiar in that the sensory rather than the motor symptoms predominate. The motor ataxia resembles the tabetic type. Rombergism is present and the reflexes are abolished. Even in this form some evidence of motor disturbance will be found, especially in the peroneal area. The chief points differentiating alcoholic polyneuritis from other types of the disorder, and from other neurological diseases, will be found in their appropriate chapters.

Needless to say, alcoholics who do not entirely renounce their habit can hardly expect to recover from this disease. Besides total abstinence, the principles underlying the treatment for all forms of neuritis obtain here.

Alcoholic "Wet Brain" or Alcoholic "Meningitis."—This is a peculiar clinical form which sometimes develops in chronic alcoholism, following the prolonged over-indulgence of spirituous liquors. It sometimes follows an attack of delirium tremens, but is by no means always ushered in thus. The writer has rarely seen a case in a female, but this is because of the more frequent indulgence by males. It is not a true meningitis but rather a serous effusion.

SYMPTOMATOLOGY.—Following an attack of delirium tremens, the patient may lapse into a semi-stuporous condition with a low, muttering delirium, or he may simply become very dull and lethargic. The temperature may be slightly elevated and the pulse rapid. The stupor becomes more exaggerated and nuchal rigidity is observed. Kernig's sign is found; the pupils are narrow and sluggish to light. The skin is rather hyperesthetic and later takes on a peculiar plasticity. The stupor deepens and incontinence of urine and feces occurs. Pneumonia often closes the scene. On the other hand, the patient may finally improve, and after remaining in this low condition for a month or so, gradually get well. The spinal fluid is found to be under considerable pressure; sometimes two or more ounces will flow. If this is examined, it will be found clear and free from cells, or nearly so, and in any puzzling case will differentiate the condition from a true meningitis. The history itself is usually sufficient to determine the diagnosis.

TREATMENT.—This should follow general lines. **Gastric lavage, colonic irrigation,** and plenty of easily digested **fluid nourishment** given often. No alcoholic stimulants should be administered, but 1/30 grain (0.00216 gram) of **strychnin** every 3 hours may be useful. In the early stages, if the patient is placed in a sitting posture, it may help somewhat in preventing the development. Lumbar puncture may also aid.

PROGNOSIS.—The outlook is not good, once the disease is fully established and the stupor and nuchal rigidity are well marked. If seen sufficiently early, however, some hope for recovery may be entertained.

CHAPTER II

DRUG ADDICTION

BY STEPHEN PERHAM JEWETT, M.D.

Opium and its derivatives, p. 18:—General considerations, p. 18:—Opium addiction, p. 18; Morphin addiction, p. 19; Heroin addiction, p. 19; Laudanum addiction, p. 20; Paregoric addiction, p. 20—Etiology, p. 20:—Predisposing causes, p. 20—Symptomatology, p. 25:—Poisoning by opium and its derivatives, p. 25:—Abstinence phenomena or withdrawal symptoms, p. 28—Diagnosis, p. 29; Treatment, p. 30:—General principles and considerations, p. 30; Drugs useful during withdrawal period, p. 36—Prognosis, p. 51; Pathology, p. 52.
Cocain addiction, p. 53:—Etiology, p. 53; Symptomatology, p. 53:—Physiological effects, p. 53; Psychological effects, p. 53—Treatment, p. 54—Prognosis, p. 54.
Paraldehyd habit, p. 55:—Symptomatology, p. 55; Treatment, p. 56.
Bromid Habit, p. 56:—Symptomatology, p. 56; Treatment, p. 57.
Chloralism, p. 57:—Symptomatology, p. 57; Treatment, p. 57.
Addiction to other drugs, p. 57.

The rapid increase in the use of habit-forming drugs within the last decade makes it an ever growing social and medical problem. Prior to ten or fifteen years ago, most drug addicts were found among those who had become enslaved to their habit through some physical disease or discomfort. At the present time the majority consists of those who have acquired the habit through social custom. These are the "pleasure users" and, in New York City alone, there can be found thousands of young persons under the age of twenty years who have used heroin or morphin for from two to five years. While addictions to drugs from the use of morphin during illness, due in a measure to a physician's prescription or administration, are becoming fewer as the years go by, those arising from social custom are constantly increasing.

But no matter which way the custom commenced, the continued use of the so-called habit-forming drugs over a period of a few weeks will result in a disease which is just as much a true disease as any other. This disease in turn produces the drug habit.

The chief difference between any habit-forming drug and a non-habit-forming drug is the fact that the former invariably locks up the secretions and excretions of the body. This gradually results in a mixed toxemia which is partly due to the drug itself, and partly due to *catabolic* products and to those of intestinal fermentation.

Inasmuch as there is a growing tendency to use narcotic drugs, it is not enough to content ourselves merely with the physical basis of the disease, important as this factor is. Even if we knew its exact pathology, we would still be helpless in preventing its spread among our young men and women. Hence the great importance of the psychological aspects of the problem. In other words, what is it which leads men to use those drugs, whose dangers they may so well know?

The whole problem is similar in its basic principles to that of alcoholism. Probably the same motive which underlies one also underlies the other. Undoubtedly the strongest bit of evidence against the pure physical basis for the disease is the fact that habitués and drinkers of years' standing show the highest percentage of permanent cures. This would not be the case were it true that the toxemia alone produced the craving for either the narcotics or the alcohol. Then, too, depending upon the physical basis alone, how could we explain the thousands of sudden cures which have taken place? The author has seen drug addicts of many years' duration, who have suddenly broken their own habits because of some intense enthusiasm; some did it because of the love of women; thousands of alcoholics of many years' standing have given up their habits suddenly because of some great religious experience, some due to other intense enthusiasms.

What do the above facts teach us? Above all, they teach us that, for the motives which underlie drug and alcoholic addiction, higher and more noble motives can be substituted. So the craving for alcohol or drugs is not a purely physical matter after all, but has its roots in the normal instincts and traits of our mental life, and it can be readily changed for some other great desire. Thus it is seen that it is not only narcotics and alcohol which must be attacked; still more important are the motives which lead to both their use and abuse.

Those who have been led into the disease through some physical disorder or discomfort are, as a whole, a higher type than are those who have acquired the disease through purely social and psychological causes. In either case the physical disease produced by the continued use of the drugs is the same, but the general outlook for permanent cures is more likely to be favorable in the former class, provided the original disorder which led to the habit can be eradicated.

OPIUM AND ITS DERIVATIVES

General Considerations.—OPIUM ADDICTION.—Opium is obtained from the unripe capsules of *Papaver somniferum.* On incision they yield a milky exudate which is allowed to evaporate. Commercially it is found as irregular flattened cakes of a brownish shade which weigh from a few ounces to about two pounds. It is semi-solid or plastic in consistency.

Opium smoking can hardly be called a habit in the same sense as is the addiction to morphin, heroin, etc. The absorption of the drug by this method is slow and many years elapse before symptoms of chronic poisoning become pronounced in the ordinary smoker, and many smoke opium only very occasionally. Then, too, there are no abstinence or withdrawal symptoms as in the case of morphinists and heroinists. For this reason one is enabled to indulge occasionally just as one would in alcohol, without necessarily becoming an addict. Those who become fiends are of the type who would become drunkards, and just as the latter practically live in saloons, the former live in the opium dens.

Before the opium is ready to be smoked, it has to be prepared. This is a very particular process, as the flavor is said to be very easily spoiled. A small piece of opium is heated on the point of what is known as a yen hok. The heat is procured from the tiny flame of a lamp filled with a peculiar oil which will not smoke when burned. After the opium has become softened by the heat, it is pulled or shied, after which it is again heated on the end of the yen hok. The bowl of the pipe is now warmed and the soft substance is placed around the small opening. The dark brown, brittle mass which is left in the pipe after smoking is called yen shi. These opium ashes are used by the Chinese for flavoring raw opium. They have a bitter taste and a sweetish odor.

Formerly the smoking of opium was rather a common habit, but of late years it has almost entirely been supplanted by sniffing of heroin. This is probably due to the high cost of opium at present, and also in part to the ease with which heroin may be procured and administered.

The action of opium does not differ from that of morphin and heroin except in degree. That of the last is the most pronounced. The symptomatology of acute and chronic poisoning from the three drugs will be taken up under one heading, as will the treatment of their addictions.

MORPHIN ADDICTION.—Opium yields or should yield not less than 9 per cent. of the alkaloid morphin. It gives to the former its characteristic physiological properties. It is most often used in the form of the sulphate.

The morphin habitué is far less common than the heroin addict in New York City. The ease with which the latter drug can be taken and the fact that heroin is somewhat more intense in its action appear to make it the favorite drug. Morphin is rarely taken except by the hypodermic route.

The general method of acquiring the habit is about as in all drug addictions. A much larger percentage of morphin addicts, however, have contracted the habit through some physical pain or discomfort. They represent a somewhat higher type than the heroin and cocain addicts, and the average age of the morphin addict is higher than that of the heroin habitué, among whom are thousands of addicts from 17 to 20 years of age.

HEROIN ADDICTION.—Heroin is the diacetyl-acid ester of morphin. It is a white crystalline powder, quite devoid of odor, and has a slightly bitter taste. Its medical usage is nearly exclusively confined to that of a sedative to the bronchial mucosa in doses of grains 1/24 to 1/12 (gram 0.0027 to 0.0054) of the hydrochlorid. It has a somewhat more intense action than morphin, although it takes somewhat longer to acquire a habit through its use, inasmuch as it does not lock up the secretion and excretion to the same degree that morphin does.

The extent and the importance of the heroin habit far exceeds that of any of the other drug addictions. Its victims are already numbered by the thousands in New York City alone, and in spite of all Federal and State narcotic laws they continue to increase.

It was previously stated that comparatively few drug addicts came originally into existence through physicians' treatment. As far as heroin is concerned, it may safely be said that it almost never does. Less than one-half of one per cent. among several thousand heroin addicts interviewed on this subject gave this as the cause of their habit. They will almost invariably tell that they became addicted through the acquaintance of another who used the drug, or as they say, "through friends" or "through bad company." It somehow appears to be a more degrading habit than morphin addiction, but this may be accounted for in part by the fact that more addicts were of the degenerate type before they acquired their habit.

Early in the habitué's career it is customary for him to take his dose by sniffing the powder into his nostrils, where it is rather quickly absorbed by the mucous membrane. It is often diluted with sugar of milk, but sooner or later he will use the full strength if he is able to get it. As the habit becomes more securely fastened upon the victim, he often resorts to the hypodermic route.

The feeling of self-satisfaction and general well-being, which the addict finds in the beginning of his career, becomes more and more difficult to obtain until he becomes nothing but a slave and takes the drug merely to feel normal. It is common for the heroin habitué to use grains xxv to xxxv (1.62 to 2.25 grams) per day when he has reached this stage. It usually takes all the money he can earn to pay for his drug and only too often he is obliged to resort to criminal practices at this stage in order to secure it.

LAUDANUM ADDICTION.—Laudanum drinking is very uncommon and is found chiefly among older persons. Less than one-half of one per cent. of those who apply for treatment for drug habit are addicted to laudanum. These few have become victims because of some chronic disease and were mostly of a neurotic type. One man, 76 years old, sought treatment, who had taken this drug morning and evening for forty years. An ounce was his usual dose toward the end and he was driven to take treatment because of its high cost.

PAREGORIC ADDICTION.—Paregoric addicts are relatively infrequent, but in certain sections of the United States it has been used in large quantities, a pint at a time sometimes being consumed. It is taken partly for the alcoholic content.

Etiology.—PREDISPOSING CAUSES.—*Individual Susceptibility.*—The fundamental instincts and traits which underlie the narcotic impulse are the same in all classes and types of individuals, but there are in general two types of organisms which are predisposed to the use of narcotic drugs and to the excessive or morbid use of alcoholic drinks. Psychology recognizes in each human being a certain *quantitative intelligence capacity* accompanied by a *qualitative affect component.* Any pathological deviation in either this affect component or in the quantitative intelligence field is likely to result in symptom behavior of an antisocial nature. Such undeveloped, defective and degenerate types and the over-sensitive, unstable types have a tendency to sublimate their mental conflicts along lower levels. They are more susceptible to their environment and are unable to transform lower into higher impulses. They are less able to stand pain, discomfort and fatigue than are those of stable nervous organization.

Let it by no means be understood that every drug addict belongs to this class. Such is certainly not the case. The following figures, obtained from two hundred cases of "repeaters," taken at random from the narcotic wards of Bellevue Hospital, upon which the author has made a rather intensive psychiatrical study, show what type of person is most likely to become a drug addict, and to remain one as long as the drug is available. These cases were studied after the patients had gone through their treatment. The author does not wish to assume that the same percentage would be obtained if every addict were studied in this manner, but experience teaches him that the 5 per cent. would be raised to a much higher figure.

There were 25 per cent. whose intelligence quotient was below 70, the majority being of the high-grade moron type; 40 per cent. were of border-line deficiency and yielded intelligence quotients between 70 and 80; 30 per cent. were of the distinctly inferior type, with intelligence quotients between 80 and 90; and only 5 per cent. could be classed as of normal adult intelligence.

The above figures do not indicate the emotional and volitional disturbances so common among them. Such affective deviates are found even among the addicts of normal intelligence capacity, and in the group studied constituted fully 90 per cent.

The following are a few abstracts from the case histories of the above:

CASE NO. 140. Male. (Voluntary admission.)

Heredity: Maternal grandmother died in some institution for the insane in Italy. Mother died of pulmonary tuberculosis. The father was a cyclic alcoholic and died at 40. Nothing further ascertainable.

Patient was placed in an orphan asylum when 6. Did not get along well in his studies. Ran away from the institution at 13. Was in Children's Court for theft at 15. Served some time thereafter in a reformatory. Never keeps any position long. Alcoholic for a few years and at 29 became addicted to heroin, for which he has taken three so-called "cures."

Physical Condition: Undernourished and anemic. Chronic bronchitis.

Mental Status: Chronological age, 33. Mental age, 12. Intelligence quotient approximately 75 per cent. (disregarding age above 16). Stanford Revision, Binet-Simon test used.

Diagnosis: Borderline mental deficiency.

CASE No. 141. Male (Self-committed).

Heredity: Father and mother separated. No other facts ascertainable.

Patient never got beyond fifth grade in school. Played truant. Has had numerous jobs, but never remained long in a place. Often discharged. Was arrested once for smashing a window. Became addicted to heroin at 22. Patient is stubborn and very irritable and troublesome in the ward. Has taken two "cures."

Physical condition: In fair general health, but has numerous abscesses due to hypodermic.

Mental Status: Chronological age, 24 years. Mental age, 11 years five months. Intelligence Quotient approximately 72 (disregarding age above 16 years). Stanford Revision, Binet-Simon test used.

Diagnosis: Affective deviate with borderline mental deficiency.

CASE No. 142. Male (Self-committed).

Heredity: Father has a very high temper, and has been arrested several times (an affective deviate). Mother is a woman of high intelligence, but has had several "nervous breakdowns" and on one occasion was in an institution. No further facts ascertainable.

Patient did pretty well in school, but did not graduate. He never held any steady position. Took up stenography and typewriting, but did not make a success. Never arrested. Tendency to "Wanderlust." Unable to control his temper at times. Very irregular sexual life. Acquired heroin habit at 19. Taken one prior treatment for drugs.

Physical condition: Subject to periodical headaches. Old gonorrheal urethritis present.

Mental status: Chronological age, 20 years. Mental age, 13. Intelligence quotient, 75 (disregarding age above 16). Stanford Revision, Binet-Simon test.

Diagnosis: Affective deviate of slightly above the borderline intelligence.

CASE No. 150. Male (Self-committed).

Heredity: Father is a hard-working and industrious man who has held a steady position at a good salary for years. Mother is a periodic drinker (affective deviate). One brother is feeble-minded and in an institution. Nothing further ascertainable.

Patient had chorea when a child. Had trouble with his teachers and left school before graduating from grammar grades. Worked at odd jobs for a few years, and then enlisted in the navy. Was dishonorably discharged for leaving without permission. Was an addict during this time but concealed it. Began to use heroin at 18. Never arrested. Quiet and well-behaved in the ward.

Physical condition: Excellent, except for an obstinate constipation.

Mental status: Chronological age, 22. Mental age, 11. Intelligence quotient, 58 (disregarding age above 16). Stanford Revision, Binet-Simon test.

Diagnosis: Mental deficiency (moron of high grade).

CASE No. 154. Male (Voluntary admission).

Heredity: Father a professor in some Western college. Mother apparently a psychoneurotic of neurasthenic type. No further facts ascertainable, except that one brother is a successful business man.

Early history of patient shows nothing unusual except that at one time during his childhood he was considered nervous and had to be taken from school for a time. Graduated from college at 21. Always very sensitive to pain and has run the course of the various irregular medical cults. Diagnosis of gastric ulcer was made several years ago at a reputable hospital. Refused operation and became a prey to all sorts of quacks. Commenced self-treatment with various anodynes and finally took to hypodermic use of morphin. Became so run down that he sought treatment for his addiction. Drug was successfully removed but he refused operation.

Mental status: Chronological age, 32. Mental age, 16 plus; intelligence quotient, 100 plus. Stanford Revision, Binet-Simon test.

Diagnosis: Normal adult intelligence with affective deviation. (Poor inhibitory control with tendency to develop substitute reactions to painful situations.)

CASE No. 160. Male (Self-committed).

Heredity: No history of mental or nervous diseases for three generations. Father and mother both maintained good health and are desirable citizens. Brothers, two in number, both successful business men.

Patient had a normal childhood and did well in school. Graduated from high school at 17. Stood well in his class. Became an actor and followed his profession a number of years. At 21 contracted syphilis and took treatment. Acquired the heroin habit at 30.

Physical condition: Pupils sluggish in reaction to light long after all drug was removed. Slight tremor of peribuccal muscles and of extended fingers present. Dysarthria noticed on different test phrases. Knee-jerks hyperactive. Wassermann, three plus in blood and spinal fluid, and colloidal gold paretic curve present.

Mental status: Aside from slight forgetfulness no symptoms were present.

Diagnosis: Dementia paralytica.

Adolescence.—Aside from these causes, there are certain others which may be classed as predisposing. The first of these is adolescence. The author has seen thousands who began their narcotic career between 15 and 18 years of age. At this period of growth in the individual, life becomes more complex, and because of some defect of constitution or environmental conditions found in certain individuals, they are at this time unable to properly adjust themselves, and this inability is expressed by drug addiction, alcoholism, schizophrenic reactions, etc.

Ease in Procuring Drug.—Another cause for the increase in drug addiction is the ease with which the drug has been procurable. The discovery of heroin has been a distinct menace. The fact that it can be taken by "sniffing" makes it a very easy habit to acquire. It can be administered at any time or place without detection of the act. Then it can be taken and passed around wherever parties of young people gather.

Carelessness on the Part of Physicians in Prescribing Morphin.—This must, of course, be mentioned as a cause, but that this is a factor in but a very small percentage of cases, the author is convinced. Less than 2 per cent. in several thousand cases interviewed in this matter admit this as the way in which they *first* took the drug. Some years ago the majority of victims of narcotic drugs attributed their addiction to this cause. This was before addiction became the menace which it surely is to-day. Carelessness, ignorance or unscrupulousness on the part of a few physicians who make a practice of prescribing for addicts with no real intention of curing them, is, of course, a large factor.

Chronic Physical Ailments.—Many chronic physical ailments have contributed to the formation of drug addictions. Among these may be mentioned renal and hepatic colic, asthma, tuberculosis, chronic alcoholism, gastric ulcer, cancer, chronic dysentery, tabes, adhesions following surgical operations, dysmenorrhea, etc.

As Relief from Sense of Fatigue.—Among the victims in the medical and nursing profession, it is usually first taken as a relief from a sense of fatigue. They tide over emergencies in this manner, get along with fewer hours sleep, and even allay the sense of hunger in this manner. Such formerly constituted a large proportion of addicts. They are now, however, a small minority in comparison to all cases, although probably numerically as large as ever.

Proprietary and Patent Medicines.—Proprietary and patent medicines containing opium or derivatives have been the cause of some addictions in the past.

There are certain facts concerning narcotic addiction among different races and nations which are noteworthy and interesting.

Race.—(*a*) *White Race.*—The drugs chiefly used by this race are heroin, morphin, heroin plus cocain, opium and cocain in the order named. About 80 per cent. of these use heroin. Hebrews, Italians, Irish and English, in the order named, are the chief offenders in New York City. Fully 40 per cent. of the addicts are Hebrews and about 30 per cent. are Italians. At least 80 per cent. of all cases are heroin users. These figures are gained from the narcotic and prison services of the hospital, however, and may not hold for all cases.

(*b*) *Black Race.*—There are comparatively few morphin addicts among the negroes. Opium smoking was fairly frequent before its high price made it prohibitive. Heroin and cocain addicts are the most frequent, but more of the former than of the latter are found in the East; in the South conditions are reversed.

(*c*) *Yellow Race.*—Opium is the narcotic most often used by this race, and usually in the form of smoking. They rarely use any other kind of drug and the use of the needle is even less common than in the negro. Probably more opium and its derivatives are used in the United States to-day than in China.

Social Conditions.—Among the drug addicts, occupations of nearly every variety are represented. Most of the addicts, however, either have no steady occupation, or are clerks, actors, actresses, stenographers, artists, sporting men, or professional men and women, of which the physicians and nurses lead the group. Among the mechanics, such as motormen, railroad men, etc., there are at present found a rather large number of addicts, and drug addiction has been and still is on the increase among this class.

No particular social class is exempt, although it is among the lower classes that it is more prevalent at the present time. The numbers among the higher classes are altogether too great, however, to stigmatize all addicts as criminals or fiends, for there are many business men, lawyers, clergymen, etc., who have acquired the disease because of carelessness on the part of physicians, or of necessity because of some chronic disorder. Few among this class have begun taking the drug for social reasons or because of abnormal or subnormal mental conditions, or because of depravity or environment. Such for the most part are morphin users, and not heroin or cocain addicts. Then, too, they keep their daily dosage to the lowest point which gives them comfort. However, they are just as much a slave of their drug, for no person can take daily doses of morphin for any considerable time without acquiring the drug disease.

Symptomatology.—POISONING BY OPIUM AND ITS DERIVATIVES.—The symptoms differ chiefly in degree of poisoning, since heroin is several times stronger than morphin, from which it is prepared.

Acute Poisoning.—It is not possible within the limits of this work to more than briefly mention some of the most important phenomena of acute poisoning. The increasing coma, extreme pupillary narrowing with sluggish reaction, pallor of the skin, cyanosis of the lips and nails, the lowering of the respiratory rate and bodily temperature are the typical signs of acute intoxication by any of the drugs mentioned above. Small doses, of course, do not bring about these extreme phenomena. Here the reaction is chiefly psychic. The intellect and imagination are stimulated. The stern realities of life are placed in the background and the person is placed in a sort of mental Utopia. External stimuli are suppressed, and if sufficient is taken, a sort of dreamy state follows.

Chronic Poisoning.—The symptoms of chronic poisoning follow after months and years of the absorption of the poison.

In the *psychic field* it is chiefly the emotional and volitional life which suffers from long misuse of the drug. The intellect does not suffer in the same degree. The patient becomes indolent, apathetic and indifferent. In many addicts, all interests in life seem to have become lost, excepting that vital one of securing sufficient drug. Pronounced ethical defects become more and more apparent and petty crimes not uncommon. In fact, the higher ethical sense becomes so impaired in the more advanced cases, that one should never trust a victim when under treatment, especially when the matter of his truthfulness is concerned. The degree of deterioration would naturally depend to a great extent upon the original personality of the addict. One would scarcely expect a man of high native intelligence and stable temperament, who had become addicted to morphin through some physical disease, to degenerate to the same extent as, for instance, a person of only border-line intelligence with an added affective deviation. It is usually those of the latter type who become the fiends. The former, perhaps with plenty of money and in good social surroundings, cannot be exactly compared to the real fiend, since he usually takes only sufficient of the drug to get along, and in addition takes good care of himself. Then, too, the kind of drug used seems to be a factor in determining the extent of deterioration of character and will. One rarely, if ever, meets an opium smoker who becomes so markedly degenerated. Heroinists and cocainists are ever so much more likely to become so, a condition which is perhaps due to the fact that the addicts of heroin and cocain are, as a rule, of a lower class. The author, in his experience, has found this to be the case.

In the *gastro-intestinal system* many changes occur. A decrease in all the secretions of the tract is found. The normal peristaltic motions become inhibited. With these changes occurring it is but natural to conclude that absorption and assimilation are interfered with. Such indeed is the case, and in chronic habitués of the most pronounced type stagnation occurs. Chronic constipation takes place and, coincident with these conditions, toxins are produced in the cecum. Consequent upon the absorption of these toxins various symptoms arise—headaches, dizziness, etc. Naturally there is a gradual loss of weight, and in the extreme cases the victim becomes greatly emaciated. Heroinists again seem to be the greatest sufferers in this respect, the opium users holding out the longest. Opium, and its derivatives to a lesser extent, seem to appease hunger. This fact of course aids in producing the loss of weight seen in these cases.

The *respiratory system* is markedly affected. Inasmuch as many heroin and cocain addicts take their drugs by sniffing, it is but natural that the nasal mucosa should suffer. A sensation of coolness or numbness is produced in the nose soon after a sniff is taken, which, of course, is brought about by the constriction of the vessels of the nasal mucosa. Dilatation is the natural result as the action of the drug wears away, and this brings about a clogging which the addict is inclined to relieve with another sniff. As time goes on the membranes become anemic and ulceration may take place. This is found particularly at the junction of the bone with the cartilaginous portion of the septum. In time a perforation may occur. In fact, complete destruction of the cartilaginous septum is seen in some cases and a saddle-nose, resembling somewhat that of the syphilitic, is found. Cocain, when administered steadily in this manner, produces these advanced changes within a relatively short time. Sometimes within less than eighteen months a perforation may take place. In the case of heroin it takes, as a rule, several years to bring about such marked changes. When the two are used in combination and taken by sniffing, the worst results of all are noticed. These changes in the nasal mucosa are of course only observed in the sniffers and they vary in intensity with the amount of the drug used and the duration of the habit. Then, too, the membranes of some addicts seem more susceptible than those of others.

Bronchitis is a very common symptom among addicts of all kinds. This results from continued use of the drugs and is found in two-thirds or more of all old cases. There is often abundant expectoration. The lung tissue in time becomes weakened and susceptibility to tuberculosis increases; this disease is often found in addicts.

Upon the *generative organs* the action of these drugs is marked. There results in the male, after continued use, a loss of sexual desire. While erection may occur, the normal inclinations are very slight. The same loss of libido is found in the female, and is usually accompanied, in time, by amenorrhea and often by dysmenorrhea. For this reason, when both husband and wife are confirmed addicts, it is very rare that impregnation takes place. Miscarriages and abortions are common. These drugs may be secreted by the lactiferous glands in a female addict and a few cases have been seen in which a nursing infant has become poisoned with the drugs through such channels. Fortunately, indeed, conception rarely takes place and abortions are common in these women. In cocain addicts, however, instead of a loss of libido there is likely to be increased desire. There are certain characteristic symptoms found in the sexual sphere which are noted during the withdrawal of the drugs. This will be considered below under the heading of Abstinence Phenomena or Withdrawal Symptoms.

The *skin* in chronic poisoning assumes a pale and sallow appearance. The marks of the needle prick in those who use the hypodermic are found and in some cases are so extensive as to appear like a rash over the entire body. Among the worst types of addicts sterilization of the needle is unknown, or if once indulged in is soon given up. They usually inject their dose through their clothes. In consequence crops of boils and frightful abscesses are frequent. Some habitués, however, will practice this filthy method for years without developing an abscess, while another who takes every precaution occasionally suffers lesions.

The *hair* for some reason takes on an increased growth. Upon just what this depends, the author is not certain.

The *general reflex excitability* is greatly diminished. Pupillary contraction with sluggish reaction to light and accommodation paresis occur. Finally, after many years, the wretched victim becomes marasmatic, and his general resistance is so lowered that he succumbs to pulmonary tuberculosis or to some other intercurrent disorder.

The above are the chief symptoms of chronic poisoning from this group. From these are to be distinguished the abstinence or withdrawal phenomena.

Abstinence Phenomena or Withdrawal Symptoms.—These occur when the morphin or heroin addict is for some reason deprived of his customary dose at the usual time. As has been stated before, they do not occur in opium smokers, except in extreme cases, when a periodic craving is observed. Often many of the symptoms which occur are partially psychogenetic in origin, since a large proportion of drug addicts are of a very suggestible type. The intensity of the reaction to the withdrawal of the drug varies greatly in different addicts. It also depends upon the duration of the addiction and the size of the doses taken. The dangers attending the withdrawal of the drug, even suddenly, are far less than is ordinarily supposed by the medical profession in general, and very much less than imagined by most addicts themselves. This pertains, of course, to those in good general physical condition. The author has withdrawn the drug within seventy-two hours in several cases of severe pneumonias occurring in addicts, without the patient ever being aware of the fact.

In all cases a few hours after the last dose of the drug, a *state of restlessness and anxiety* ensues which varies greatly in different subjects. In some cases it is so mild that it is hardly noticed, but in others it assumes the nature of a wild and maniacal frenzy. Occasionally clouding of the sensorium occurs, with visual and auditory hallucinations, chiefly the former.

Soon the *pupils,* which were hitherto contracted, have become *dilated and often unequal.* Accommodation paresis appears. The secretions which were formerly inhibited have by now become more or less profuse, so much so that lacrimation and running of the nose occur. The gastro-intestinal tract becomes active. Griping pains in the abdomen are frequently observed. In place of the former constipation, the stools become watery, and even bloody in some cases. Yawning, sneezing, coughing, vomiting and retching take place rather spasmodically. Various vasomotor disturbances, such as rushes of heat to the head, cold hands and feet, pallor and cyanosis often occur. The pulse becomes soft, rapid in rate—90 to 140—often dicrotic and in cases of cardiac weakness, irregular, finally imperceptible, and collapse threatens.

Various kinds and degrees of *pain* are complained of—in the legs, back, epigastrium, etc. Paresthesias, trigeminal neuralgia, tremors and ataxia sometimes occur.

The *sexual functions* again become active, and in women the menses reappear and are often profuse. In the male, nocturnal pollutions become very troublesome in many cases, and may occur for a considerable period. Sexual excitement often becomes intense in both male and female.

Summary.—As stated before, all the above symptoms vary in kind, duration and degree in different addicts. Dangers only threaten those in very poor physical condition and in cases of cardiac weakness.

The first depends in a very large measure upon the nature of the drug used and the method of administration. Opium smokers and opium eaters may go on for years without many signs or symptoms of a troublesome nature. Heroin users suffer much more, and reach the terminal state much sooner than morphinists, although it takes somewhat longer to create a real habit by the use of heroin. It also depends greatly upon the make-up of the individual, and upon his social and financial condition. Those who are obliged to neglect their diet and their general mode of living because of the cost of maintaining their habits, and those who practically live on the drug soon constitute human wrecks. Within two or three years, in some cases, they become undernourished and anemic and fall prey to pulmonary tuberculosis or some other disease, or die of the poison itself. Others who have plenty of friends and money may continue in a fair degree of physical health after twenty or thirty years of morphin addiction.

Diagnosis.—This is not always as easy as might be expected, when one considers the mistakes that are made. These are usually seen in misidentifying something else as a drug addiction rather than in mistaking a drug addiction for some other disorder. It is not at all uncommon, for example, for a person suffering with some psychosis to be sent to the psychopathic ward of Bellevue Hospital, with a diagnosis of drug addiction. Several schizophrenics have thus been brought in during the past year. Two advanced paretics and several cases of alcoholic hallucinosis were sent in with a diagnosis of morphin-poisoning. Cases of coma arising from injuries to the brain, from apoplexy, uremia, alcoholism and following convulsions from any cause have to be differentiated from acute poisoning with any of the narcotic drugs, particularly opium and its derivatives.

The drug should be carefully searched for on the person or clothes of the suspected patient. The skin should be examined for hypodermic marks, scars or abscesses.

The symptom which is usually first noticed is the pupillary contraction with its attendant sluggishness to both light and accommodation. As the pupils vary somewhat from this picture when the action of the drug is waning, one should also suspect a widely dilated pupil which is also sluggish in reaction. Often, too, certain mydriatic drugs, such as atropin, cocain or hyoscin, are used in combination with the opiates; but in these as well the pupillary reactions are distinctly modified in character.

Certain variations in mood are characteristic of drug addicts. At times they are dull, drowsy and sleepy while, in a short space of an hour or less they are filled with animation. Any of the symptoms noted under Symptomatology are indicative of drug addiction, but are not diagnostic.

A forty-eight-hour period of observation under conditions which absolutely insure against the suspect getting his accustomed doses of the narcotic drug will soon result in a confession, even though he is at first able to conceal his symptoms. If no symptoms whatever arise during the first few days, the observer may be sure there is no narcotic drug disease. When cocain has been used in addition to the opiate, no particular symptoms aside from drowsiness or sleep will be noticed for nearly twenty-four hours. This is because the stimulating effect of the cocain has counteracted the narcotic effect of the other drug. Those who come to the narcotic wards with a cocain and morphin or heroin addiction are always very drowsy for many hours and do not show the withdrawal symptoms as early as those who have used the opiate alone.

Treatment.—General Principles and Considerations.—*Should be treated as a disease:* There are a few basic principles which one must thoroughly comprehend in order to successfully treat drug addicts. The first and most important is the *attitude toward the patient* and the addiction. The physician must not make the assumption that the victim has no disease, and consequently recognize no pathology. If he does assume this attitude he is likely to treat the patient as a criminal, and the chances of permanently aiding the unfortunate would be few indeed. It is true that there are many addicts among criminals—probably about 3 per cent. of all criminals in this country are drug cases. These constitute, however, but a very small part of all drug addicts and even among the criminals there is a pathology present to be reckoned with.

He must recognize these two facts: first, that the patient is suffering from a true disease—a mixed toxemia; second, that the personality behind the disease may also be pathological, and that in many it requires treatment fully as much as does the body itself.

No specifics for cure of addiction: Furthermore, he must know that there are no "specifics" for this disease. That is to say, there are no specifics in the sense that quinin is a specific for malaria, mercury and arsenic for syphilis, diphtheria antitoxin for diphtheria, etc. What specific could one hope to find for a toxemia of a complex nature and of such a complicated origin? It consists of not only the drug itself, but of poisons arising from nearly every gland and cell in the body, from intestinal fermentation, etc. Even though there were a specific for the physical basis of the disease, how could we apply it to the faulty mental roots of the disorder?

No ideal routine treatment: Again, there can never be any perfect routine treatment which can apply to all cases. The general principles underlying the treatment is the same for all, but each case is a problem unto itself. This applies not only in the different degree of reaction to the drug used in the treatment, but especially to the different psychic reactions.

Institutional treatment best: Whether any addict should be treated for his habit as a regular office patient is perhaps debatable. In the opinion of the author, it is a very questionable procedure, however, and the more he knows of the disease and the ways of drug addicts in general, the more questionable it becomes. Institutional treatment has decidedly the most to commend it, but if this is impossible, it may be carried out in the home of the patient under certain conditions where trained and trustworthy nurses can be in constant attendance day and night. A well-equipped sanitarium is the best place to carry out the treatment because here the proper measures during convalescence can be properly executed.

Question of the veracity of addicts: All drug addicts are not liars, contrary as this is to the opinion of many. When it is a matter of getting their accustomed drug, however, there is not one of them who would not lie provided there were a little suffering or discomfort present. In this matter they are absolutely irresponsible, as a class, and consequently during this treatment, and especially the early days of the same, not one of them should be trusted in this matter. As truthful and honest as an addict may be in any other matter, he will lie and practice all kinds of deceit concerning his drug, and in order to obtain it he will resort to the most extreme and disgusting measures.

A few of the various ways in which addicts have tried to bring drugs into the narcotic ward or to have it brought in will illustrate how careful one must be on this point. These are some of the experiences which have come under the author's own observation and they could be multiplied a thousandfold by the experiences of others.

A lawyer, forty-eight years old, graduate of a leading American college and of one of our best universities, presented himself for treatment. He had acquired some prominence in his profession and was a man of culture and refinement. One would surely not brand this man as a degenerate and liar in general terms: Particularly one would be likely to trust him in the matters concerning his treatment, inasmuch as he applied voluntarily for it, and even went so far as to have himself committed to the hospital by the court. As is the custom in all cases, before he went to the ward his clothes were removed, and a cleansing bath given to him. On the second day of his treatment, when a high colonic irrigation was ordered, he became so upset and objected so vigorously that a rectal examination was made—two full vials of morphin were found. This man declared he would never have used the drug except in the event of suffering. This was no doubt true. He has remained well, however, to this day, and the chances of his remaining free permanently seem quite certain.

A female addict, also a voluntary admission, managed to smuggle 60 grains of heroin and a hypodermic set into the ward concealed in her vagina. This is not at all uncommon. It has been found stuck to the hair under the arms; in papers glued to the inner surface of the thighs; on the soles of the feet, etc. All possible ways of smuggling in the accustomed drug in the clothes are practiced—beneath the layers of leather on the soles of patients' shoes; in false pockets inside the shoes and in the heels; in the lining of their clothes; in the bands of their hats, and in other ways too numerous to mention.

Just as cunning methods of sending the drug into the wards by the friends of the patients are seen. It has been sent in, in powder form, beneath stamps on letters; in a false pocket in the fly of an envelope; in cigarettes; and concealed in the binding of books. Fruit is a favorite method of trying to send in drugs. In one case, a banana had been so artistically employed as to escape detection. Drugs are concealed in fruit of all kinds and in varieties of ways.

If those of the better type, who apply voluntarily for admission, will resort to such deceit, one can see how important it is to be on the alert in this respect with all addicts under treatment.

Not all degenerates and perverts: The public and many of the profession have been taught to regard all drug addicts as degenerates, perverts, criminals, liars, etc. This is very far from the truth, the fact being that some are of this type, and some are not. The mere use of drugs over a long period does not necessarily lead to moral degeneracy or perversion. Thousands of patients who have used morphin for years have still maintained their integrity and honor in the community and have made good wives and mothers, husbands and fathers whose characters are beyond reproach. This forces us to look for some other explanation for those traits of character which, being present in a good many addicts, leads the world to consider them all degenerate.

The man who presented defects in character and morals before he became an addict is the one who presents them, perhaps more markedly, after years of addiction. It is this type of real drug fiends who are constantly before the public. Their various offenses and crimes have so often been brought before the public notice that both physicians and lawyers are prone to look upon all addicts as belonging to this class. There are probably more of this type at the present time than formerly. The majority of heroin and cocain fiends are of this type. This is not because the drug has made them such, but because heroin and cocain are so easy of administration and have been so easy to procure during the past few years that the increased number of this type has been inevitable. When such as these are so situated that they can no longer get the money to buy this drug, they will lie, steal, and even commit more serious crimes in order to get it. Others of the criminal class would commit all manner of crimes whether or not they were drug addicts, although, if they were such, their offenses might become more numerous and more serious because of the effects of the drug.

So it is seen that it is the financial condition of an addict which to a large extent determines his conduct. He does not lie, steal, etc., because of any physiological nature of the drug but because his suffering from withdrawal drives him to commit crimes if he cannot procure the drug in any other way. So long as a man of good character can procure his drug unmolested by any one, he will be able to retain his integrity and his business and social standing. If fortune were unkind to him, however, and he no longer had the means to buy his narcotic, he would then resort to any deception or theft to obtain it, at least in most cases. The same man would do the same thing if he were starving for food or dying of thirst if he had no other way of supplying his want. He could not on this account be classed as a degenerate and criminal. What is nearer the truth is to state that drug addiction is potentially capable of making a man a liar or a thief but that it does not always of necessity do so.

Confidence of patient and control of his surroundings important: What has been hinted at regarding these factors must be emphasized. The confidence of a patient in his physician is important in any case, but in narcotic disease it is absolutely necessary for good results. So, too, is the control of the patient. Self-preservation is a strong motive for human conduct, and one could hardly expect a drug addict to want to suffer from the effects of withdrawal of the drug if he could easily obtain it. This illustrates the inconsistency in treating the addicts as office patients.

One might divide all drug addicts into two classes: one in whom the addiction is principally a physical disease; the other, in whom, in addition to the physical element, there is an absolute mania for the drug. In the second class of addicts the whole life interest is to secure control of his drug. He gets to think that he could not possibly live without it; every little ache or pain or discomfort of any sort which he suffers when not under the influence of the drug he attributes to this fact; he actually believes that he would die if he were deprived of it, and that nothing could possibly take its place; he also believes that he would suffer the agony of the damned before he died, and he is determined in his conviction that only more of the drug could save him from this fate. He feels that he knows more about drug addicts and all matters touching upon this, than all the physicians past and present. There is a large percentage of cases of just this type, and the treatment of them is filled with difficult problems. The mental side of the treatment is of such importance in this type of cases that the physical is a minor part in the treatment. When confronted with this type of case go into detail as to all the important facts in the patient's life history, particularly as related to his habit. Find out the exact reason which first prompted him to resort to the drug and why he continued with it until it became a habit. Find out just why he came to you for treatment and what treatments, if any, he has previously taken and with what results; ascertain the nature of the treatments, how much he suffered and how long; also why he resorted again to the drug. Make even a deeper study if possible and by psycho-analytic methods unearth some of his hidden complexes. In other words, endeavor by every means to understand the patient's mental life. By this time you will have learned just how little faith he has in you or in anybody else as far as hopes for a cure are concerned.

However, if he still has a little hope, it is now your duty to increase it by giving him all the encouragement possible. Impress upon him firmly the fact that his chances for a permanent freedom from his slavery are not only probable, but quite possible if he really desires this freedom. Tell him there will be almost no discomfort in the treatment you will give him, and relate the experiences of other successful cases. If possible let him talk with one who has been restored to his health and freedom, and from him find out how much it has meant to him and with what little suffering it was accomplished. The patient will be glad to hear all this and he may by this time gain more confidence in you. The next step to aid in establishing his confidence, and to aid in the physical treatment of the case, is a most minute and painstaking medical history and physical examination. Use all the instruments of precision which you can command. Take his blood-pressure and examine his blood and urine. He will see that you are thorough in your methods and an up-to-date physician, and his confidence in you will grow.

Explain to him the pathology of his disease in so far as possible and show him the meaning of his past suffering during withdrawal. Show him that you have a thorough knowledge of the subject in general, and of his case in particular. You are now ready to begin the physical treatment.

First, give the patient a cleansing bath, preferably a **vapor bath** if the patient is in fit condition, after which a cleansing **enema** should be given. See that the patient drinks plenty of pure cold **water** at frequent and regular intervals. Find the exact daily dosage and the kind of narcotic usually taken, and continue this dosage for a couple of days, while the preliminary measures above indicated are carried out. We are now ready for the elimination process and the rapid reduction of the drug.

Elimination and methods of securing it: We must keep in mind the pathology of the disease, and remember that the cells of the body are simply bathed in toxins which must be eliminated through the skin, the kidneys and the bowels. It is chiefly through the bowels and kidneys that this elimination is secured. The question now arises just how this may best be brought about, for it must be borne in mind that members of the opium group suspend peristalsis, and in some cases this motor function is almost paralyzed. Consequently, any purgative drug which is to be given should contain a motor stimulant, or else a motor stimulant may be given separately. **Strychnin** fulfills the requirements in this respect better than any other drug, as was suggested by Dr. George E. Pettey of Memphis, Tenn., after a long and successful experience with the drug. The principles of purgation in these cases, as advised by Dr. Pettey, can be followed with safety and great satisfaction.

The combination which he recommends and which the author has used with excellent results is the following:

℞

Hydrargyri chloridi miti (Calomel) Rhamni purshianæ extracti (Cascara)	āā grains x	(0.65 gram)
Ipecacuanhæ	grain i	(0.065 gram)
Strychninæ nitratis	grain 1/4	(0.0162 gram)
Atropinæ sulphatis	grain 1/50	(0.0013 gram)

M. and make 4 capsules.

As Dr. Pettey points out, the strychnin content of this formula may appear very high, but when the absolute lack of normal peristalsis, which is noted in these cases, is taken into consideration, the necessity for so large a dosage is seen at once. Furthermore, experience teaches the safety and value of this practice, and it is well known that the doses of this drug which have hitherto been recommended are altogether too small in nearly all cases. In fact, the addition of more strychnin is required in certain addicts.

The author has been accustomed to follow quite closely the directions which Dr. Pettey recommends for the use of this formula, since much experimentation has shown that it cannot be improved upon in most cases. One such capsule should be administered at 4, 6, 8 and 10 P. M., after the evening meal. At 6 A. M., 1/30 grain (0.00216 gram) of strychnin is to be given by hypodermic, and either 2 ounces (59.2 c.c.) of castor oil, a bottle of magnesium citrate, or some other saline cathartic. The above should be repeated at 8 A. M. and again at 10 A. M., if good results have not been obtained. No breakfast is to be taken the morning the treatment is being given. Neither should any of the accustomed drug be given until after thorough purgation. This usually occurs, in most instances, by 9 or 10 A. M. at the latest. One-half the usual dose of the narcotic may then be given.

The next step in the treatment consists of the **infusion into a vein of about a quart of normal saline solution.** It is well to explain to the patient fully its rationale. This is given with the purpose of diluting the toxic substance in the blood stream and to replace rather rapidly the loss which has been brought about by catharsis, and also to bring about elimination through the kidneys. High blood-pressure and arteriosclerosis are contra-indications. It is best given at 3 P. M., the patient being put to bed for a few hours after the infusion. A light supper is given, but no cathartics that night. The next day at 4 P. M. a purgative capsule is again given, and repeated at 6, 8 and 10 o'clock. No supper is taken that night, and on the following morning, at 6 A. M., again 1/30 grain (0.00216 gram) strychnin by hypodermic, and oil or salts should be given. These are to be repeated in two hours, until thorough results are obtained. No morphin is to be given until the bowels have acted. By this time it will be found that the patient can get along quite comfortably on one grain (0.065 gram) or less, divided into three or four doses during the twenty-four hours. In the afternoon the quart of normal saline is injected into a vein.

From this time on, one has to be guided entirely by the individual patient in carrying out the treatment. In the cases of short duration, especially of patients who have been taking this drug by sniffing, no more morphin will be required. In others it may be best to reduce the dose still further for four or five days until an almost infinitesimal quantity is given at a dose, after which a sterile saline solution may be used for a day or two and then all hypodermic injections stopped. In still others it will be necessary to resort to the use of **hyoscin** to tide over a few hours of discomfort which certain patients will not tolerate. It will require comparatively little of this drug to accomplish its purpose if proper eliminative measures have been carried out. The inclusion of a few case histories will best illustrate the proper use of this drug, although the use of hyoscin in drug addiction will be more fully treated elsewhere.

After the patient has been put through this treatment and has been getting on without his drug for a day or two, he will in a great many instances state that he never felt so well in his life and will also look the part. Unfortunately the patient will frequently insist upon leaving the institution at this point, and often nothing can induce him to remain. If he is a person of strong character, he may remain away from the drug from this time on. More often, however, if he does leave at this period, he will fall in with his old associates within a short time and again be induced to trifle with the drug, acquiring the habit anew within a few weeks. It is for this reason that **convalescence should take place in a sanitarium,** where the body may be restored to the soundest possible health and where at least a month or two will **separate him from his old life.** He will then be in a position where he will not be again driven to the use of the drug, except through his own constitutional instability, and if this inferiority does exist the same conditions which were operative in making him a drug addict in the first instance will surely operate again, if they are met with, and nothing short of his permanent isolation or his total inability to get the drug will prevent a recurrence of the habit.

DRUGS USEFUL DURING WITHDRAWAL PERIOD.—*Strychnin.*—This is the most useful single drug used in these conditions and there is no other drug which can replace **strychnin,** especially in the more chronic addictions.

Its chief indication is as a motor stimulant to the intestinal tract. Until one has had a rather extensive experience with strychnin in these cases, one is inclined to be afraid of giving it in sufficient dosage. As given in other conditions, in doses of 1/60-1/30 grain (0.001-0.002 gram), it is useless. It must be pushed until results are obtained, and it is surprising how much will be required in some cases. No two cases will require the same amount to get the correct effect. The more chronic the addiction and the more obstinate the torpidity of the bowels, the more it will take. It is the most important single ingredient of the purgative capsule which Pettey recommends and which the author has used very successfully in his own treatment of the morphin and heroin disease.

Spartein Sulphate.—This drug in proper dosage either by mouth or by hypodermic is very valuable. After the active treatment is over and the feeling of weakness comes on, no other drug, except morphin itself, gives the same results as **spartein sulphate.** It buoys the patients up and gives them "heart" during a very trying period. The usual dose given is often much too small. At least 2 grains (0.130 gram) are required for correct results.

Hyoscin.—This drug is very useful in many cases, but should not be used indiscriminately. It is not a specific as some are inclined to believe. In those patients who are particularly intolerant to all pain and discomfort, **hyoscin** is useful in the same sense that ether is useful during a surgical operation. If it were practical to keep a patient under chloroform or ether for from thirty-six to forty-eight hours, these would serve a similar purpose. In many cases it is not necessary to resort to hyoscin at all; in others only a little will be required; while in others, a considerable amount will be required. It is only as one gains experience with its use that one can be properly guided. In all cases where the proper preliminary measures have been carried out, *i.e.*, good elimination from bowels and kidneys by the right use of strychnin, cathartics and saline infusion, very much less hyoscin will be needed, if it is used at all.

Aspirin.—For its analgesic effect this drug is often useful in these cases in 10 grain (0.65 gram) doses. The pains in the legs often observed during withdrawal are favorably influenced and the patient made more comfortable. **Aspirin** takes the place of phenacetin, antipyrin and other drugs of this class.

Other Drugs.—Many other drugs have been advocated in the treatment of drug addictions, but faithful trial by the author has found them all wanting with the exception of certain purgatives and the saline cathartics which are used in conjunction with or following strychnin in large dosage.

CASE HISTORIES AND CLINICAL NOTES.—The following cases will bring out the facts that no two persons can be treated exactly alike. Some can have the dose of the drug reduced much more rapidly than others; some require more purgatives. The notes will also show the difference in susceptibility to hyoscin and will illustrate very clearly how some cases will require none, some little and others considerable of this drug during the withdrawal period.

CASE I.—J. R., male, age 25 years, machinist; weight 133 pounds, height 5 feet 6 inches. Admitted to narcotic wards of Bellevue Hospital as a voluntary case. Began the use of heroin about four years ago and has used it continuously from that time until admission. Now uses 20 grains (1.3 grams) per day by nasal route. Occasionally uses the needle. This patient's general health was fair. He had lost fifteen or twenty pounds in weight during past six months and was beginning to feel weak and listless. Heart was normal, nasal mucosa anemic, and a few ulcerations noticed. Slight bronchial catarrh. Kidneys normal. Very constipated.

April 16.—Patient was admitted at 2.15 P. M. and was "loaded." (This is the expression the nurses use when a patient enters who has taken an overdose prior to entrance.) After the usual bath and search, he was placed in the wards and allowed to remain up. Nothing in the way of drug or medication was given him until 6 P. M., when Specific No. 10 (*sterile water* *) was given by hypodermic and repeated every two hours through the night. Nurse's notes stated that he passed a fairly comfortable night and slept considerably.

Had the patient entered showing withdrawal symptoms the procedure would have been somewhat different. Experience has taught that when patients enter "drunk" with the drug, there is no use giving them any more till it is really necessary, although, if they think they are getting nothing, they fret and fume very much, and some manifest considerable psychic discomfort.

---

* "Specific No. 10" is used as a name for sterile water. Patients sometimes see their charts, and the psychic effect of the hypodermic is lost when they realize that they are receiving sterile water.

April 17.—Temperature 98° F. (36.6° C.); pulse, 80; respiration, 18. Was up all day and quite comfortable on Specific No. 10 given every two hours. Had a fair appetite and made no complaints. Some treatment continued through the night. Notes state that the night was very quiet, but patient commenced to complain toward morning that the "shots" were not "holding him."

April 18.—Patient commenced to get quite restless and uneasy and asked if the dose he was getting could not be raised. Was starting to show withdrawal symptoms and was given Magendie's solution, minims 10 (0.60 c.c.), every two hours until 4 P. M., when Specific No. 10 was substituted. A capsule containing the special purgative was given at 4, 6, 8 and 10 P. M. No supper was given. The patient spent a fair night.

April 19.—At 6 A. M. strychnin, grain 1/30 (0.002 gram), was given by hypodermic and castor oil, 2 ounces (59.2 c.c.). No result; same dose of strychnin and castor oil was repeated at 8 P. M. No breakfast. Four large and free movements occurred during the day. Magendie's solution was cut to 8 minims (0.50 c.c.). Slight nausea, but no vomiting. Was slightly uncomfortable but said he could stand it on the dose he was getting. No marked withdrawal symptoms present. At 2 P. M., 900 c.c. normal saline solution were introduced. Magendie's solution, minims 8 (0.50 c.c.), was continued until evening, when it was reduced to minims 6 (0.36 c.c.) Slept at intervals and did not complain.

April 20.—Continued on Magendie's solution, minims 6 (0.36 c.c.), every two hours. Showed no marked withdrawal symptoms, but was decidedly restless. No supper given. Purgative capsule given at 4, 6, 8 and 10 P. M. Specific No. 10 given every two hours throughout the night.

April 21.—Strychnin, 1/30 grain (0.002 gram), and castor oil, 2 ounces (59.2 c.c.), at 6 A. M. Large and free movements of bowels at 8.30, 9, 11.20 A. M. and 12 M. No more morphin was given, but hyoscin, grain 1/100 (0.00065 gram), was given at 1 P. M. and at 1.15 P. M. A third dose was given at 2 P. M. Patient slept about two hours. At 4 P. M normal saline solution, 800 c.c., was injected into vein. Refused any more hypodermics and thought he could get along without them, which he did. Was given trional, grains 15 (0.972 gram), and sulphonal, grains 15 (0.972 gram), in hot milk at 8 P. M. Slept about six hours. Only complained of weakness.

April 22.—Elixir iron, arsenic and strychnin before meals and spartein sulphate, grains 2 (0.13 gram), every four hours for two days. Gained in strength daily until he left the hospital on April 25th to go to the country. Reported a month later; is in excellent health and has no desire to go back to his habit so far, although this is no guarantee that he will not use the drug again when thrown into his former bad environment and among his old associates.

Case 2.—B. S., male, age 22 years, railroad operator; weight 155 pounds, height 5 feet 5 inches. Admitted as a "voluntary" committed case through the Board of Health. Stated that he had used about 15 grains (0.972 gram) of heroin per day for a year and a half. Has used the needle at times during the past few months.

On admission he was rather restless and was beginning to show withdrawal symptoms—running at nose, sneezing, pains in his legs, etc. General health was very good.

April 29.—Day of admission. At 2 P. M., half an hour after admission, patient was given 1½ grains (0.098 gram) morphin sulphate, and at 5 P. M. the same dosage was repeated. As patient remained uncomfortable and complained of withdrawal phenomena, the dose was raised to 2 grains (0.13 gram) morphin sulphate at 8 P. M. He slept fairly well through the night.

April 30.—Was kept comfortable through the day on 2 grains (0.13 gram) at 9, 2 and 7 P. M. At 4, 6, 8 and 10 P. M. the purgative capsules were given. Was rather restless all night. Slept very little and complained that he needed more drug. An injection of sterile saline solution (hypodermic) was administered at 4 A. M. which satisfied him until 10 A. M., when he became so restless and uncomfortable that 1½ grains (0.098 gram) morphin sulphate was given.

May 1.—No breakfast. At 6.30 A. M. grain 1/30 (0.00216 gram) strychnin sulphate and bottle magnesium citrate were given. No result. At 8.30 A. M. strychnin sulphate, grain 1/30 (0.00216 gram), and 2 ounces (59.2 c.c.) castor oil were given. Complained considerably and was nauseated. Strychnin sulphate, grain 1/15 (0.00432 gram) at 10 A. M. Bowels moved copiously and freely at 10.15, 10.30 A. M., 12 M. and 12.45 P. M. Felt very much better, but weak. Normal saline infusion 900 c.c. at 2 P. M. Rather restless during the afternoon. Grain 1 (0.065 gram) morphin sulphate at 7 P. M. Slept off and on during the night. Became quite restless towards morning and a hypodermic of sterile saline solution was given which kept up his courage.

May 2.—Was kept fairly comfortable during the day with grain ½ (0.0324 gram) morphin sulphate at 10 A. M., 3 P. M. and 8 P. M. Purgative capsules again at 4, 6, 8 and 10 P. M. Slept about five hours during the night.

May 3.—No breakfast. Grain 1/30 (0.00216 gram) strychnin at 6 A. M. and castor oil, 2 ounces (59.2 c.c.) Copious stools at 8, 8.40, 10 and 10.30 A. M. Slight nausea. Slept about two hours and ate a light lunch. Commenced to complain of need of drug. General condition very good. Temperature 98.4° F. (36.89° C.); pulse, 98; respiration, 24; blood-pressure, systolic, 140; diastolic, 110; pulse-pressure, 30. Saline infusion at 2 P. M. Patient put to bed and grain 1/200 (0.00032 gram) hyoscin given at 2.30, 3 and 4 P. M., and grain 1/100 (0.00065 gram) at 5 P. M. Slept soundly until 9 P. M. Bowel movement at 9 P. M. Had a glass of water. 9.30 P. M. given hyoscin, grain 1/100 (0.00065 gram), 10.30 P. M., grain 1/100 (0.00065 gram) hyoscin. Slept until 1 A. M., when he aroused and complained of thirst. His mind wandered slightly, but could answer questions, and said he was feeling pretty comfortable except for a dry feeling in his throat.

At 2 A. M. complained of feeling uncomfortable, and was given grain 1/200 (0.00032 gram) hyoscin. Pulse, 110; respiration, 26. Bowels moved at 2.30 A. M. Hyoscin given at 3 A. M., grain 1/200 (0.00032 gram), and at 4 A. M. same dose. Slept until 7 A. M. Was slightly restless on awakening, and was mildly delirious.

May 4.—Awakened at 7 A. M. and was restless. Asked for water and drank two glasses of it. Voided urine .2 c.c. pills. At 8 A. M. grain 1/200 (0.00032 gram) hyoscin. Slept until 11 A. M. Said he felt comfortable, but mind was not yet clear. Asked for food. Milk toast at 12 M. At 2 P. M. mind was quite clear and patient's only complaint was some aching of legs. Refused any more hypodermics. Phenacetin, grains 10 (0.65 gram), at 3 P. M. Free bilious movement at 3.30 P. M. Complained of weakness, but wanted no more morphin. Hot soup with toast at 6 P. M. Slept until 8 P. M., and had glass of water. Small bowel movement. Slept at intervals during the night.

May 5.—Had light breakfast of hot cocoa and toast at 7 A. M. Glass of milk at 10 A. M. Remained in bed most of the day, and complained of weakness. Did not ask for drug, but admitted that he would use it if he had it, because he felt weakness. Grains 1½ (0.097 gram) spartein sulphate at 12 M. This "braced" the patient considerably and was repeated at 2 P. M and at 7 P. M. At 8 P. M. sulphonal, grains 15 (0.972 gram), and trional, grains 15 (0.972 gram), in a glass of hot milk were given. Slept six hours.

This patient remained in the hospital until May 12, and felt very well on discharge. Was eating and sleeping normally and had no desire to use the morphin. Went immediately to an institution in the country where he remained two weeks and reported that he was gaining daily in strength, and was anxious to return to the city to resume his work.

CASE 3.—B. J., male; age 27 years, clerk; weight, 140 pounds; height, 5 foot 7 inches. Admitted as a voluntary case to narcotic ward of hospital. Has used heroin in gradually increasing doses for three years for pleasure. At present, uses about 20 grains (1.3 grams) per day by "sniffing." Has used cocain occasionally, but is not using it at present.

Was beginning to show loss of strength and had lost 25 pounds in weight during past year. Heart, lungs and kidneys normal. Slight bronchial catarrh. Skin, a bad color. Very constipated. Said he had about one good bowel movement a week. Temperature, 98.6° F. (37° C.); pulse, 80; respiration, 20. Chief complaint was that he "couldn't stand anything." Said that he had had enough of "drugs" and would do anything to be cured.

March 1.—Admitted at 10 A. M. Was slightly uncomfortable on admission as he had "run out" of heroin several hours before coming to the hospital. Given a bath and an enema and placed in the ward. Asked for a hypodermic. Was given Specific No. 10 (sterile water), minims 10 (0.6 c.c.), by hypodermic every two hours. Rather restless, but did not complain. Ate a good dinner, but no supper was allowed. At 4, 6, 8 and 10 P. M. he received the purgative capsule containing calomel, ipecac, cascara, atropin and strychnin. Was given morphin sulphate, grain ½ (0.0324 gram), at 8 P. M. and the Specific No. 10 every two hours through the night, with exception of two doses when he was asleep.

March 2.—Rather restless on getting up. Had strychnin sulphate, grain 1/30 (0.002 gram), and ounces 2 (59.2 c.c.) castor oil at 6.30 A. M. Asked if his dose could not be raised, as it was not holding him very well. Was told that it would be raised, but was continued on sterile water by hypodermic every two hours. Bowels did not move. Was given strychnin, grain 1/30 (0.002 gram) and ounces 2 (59.2 c.c.) castor oil at 8.30 A. M. Vomited about 9 A. M. a large amount of bilious fluid. Was given grain 1/15 (0.004 gram) strychnin at 10.30 and a bottle of magnesium citrate. Bowels commenced to move freely and copiously at 12 M. and continued several times during the afternoon. Commenced to feel very much better. Was given 1,000 c.c. normal saline solution intravenously at 2 P. M. and put to bed. Specific No. 10 continued every two hours through the night. Was decidedly improved in appearance. Skin clear; color good. Appetite returning.

March 3.—Ate cereal, cocoa and toast for breakfast. Bowels moved at 9, 9.30 and 12 M. Refused hypodermics as he felt they had been reduced to a point at which he could get along. Was told that he had received only morphin, grain ½ (0.0324 gram), since he was admitted, and that the hypodermics were a substitute. This he could hardly believe. At 3 P. M. he commenced to complain that he was feeling weak and grains 1½ (0.097 gram) spartein sulphate was given by hypodermic. This seemed to brace him up. Ate a good dinner at noon, but no supper was allowed. At 4, 6, 8 and 10 P. M. the purgative capsules were given. At 8 P. M. trional, grains 15 (0.972 gram), and sulphonal, grains 15 (0.972 gram), were given in hot milk. Slept until 4 A. M., when his bowels commenced to move.

March 4.—Ounces 2 (59.2 c.c.) castor oil at 6 A. M. Ate light breakfast. Spartein sulphate, grains 1½ (0.097 gram), at 9 A. M. Bowels moved six times during forenoon. Normal saline infusion, 800 c.c., at 2 P. M. Slept nearly the whole afternoon. Said he was beginning to feel better than he had in a year and he could not be induced to remain in the hospital any longer.

This patient went home with the best of intentions, and if he could have been placed in the right surroundings, things would have gone well. When he got home he was feeling weak, as would be expected. He met his former companions, who induced him to take a little drug to "brace him up." He had the sense to return to the hospital the next day and tell his story, was admitted, and remained a week and then was sent to the country. At present he is doing very well and is in the best of health. This is a common story with many who insist upon leaving the hospital too early. Many of them leave with the best intentions, only to meet some addict on the way home. Others, however, leave after this preliminary treatment and have sufficient stability to withstand any temptation ever to touch the drug again. This shows the absolute necessity for prolonged convalescence under proper surroundings. Even under such excellent conditions some will be led to return to the drug because of the same reasons which induced them to touch it at first.

CASE 4.—T. L., male, age 29 years; ex-soldier; weight, 150 pounds, height, 5 feet 10 inches. Admitted as a "voluntary" committed case, *i.e.*, he applied for commitment to a city magistrate who sent him to Bellevue for treatment. Has been a "pleasure user" of heroin for four years and was discharged from the army on that account. Uses grains 15 (0.972 gram) per day at present, by the hypodermic method. Has reduced himself to about 5 grains (0.324 gram) a day on several occasions, but never got any lower.

Patient's general physical condition was fair, although he had lost a little weight, had a poor appetite, and was constipated. Heart, lungs and kidneys normal. Skin, sallow. Tongue coated and breath offensive. Said he tired very easily and had to take a dose of heroin before he attempted any great exertion. Temperature, 99° F. (37.2° C.); pulse, 80; respiration, 24.

March 9.—Entered hospital at 2 P. M. Was somewhat restless and uncomfortable. Was given sterile water, minim 10 (0.6 c.c.), by hypodermic at 2.15 P. M., and every two hours, until 9 P. M., when he commenced to complain of pains in his legs and cramps in his bowels. At 9.30 P. M., morphin sulphate, grains 1½ (0.097 gram), given by hypodermic. Slept nearly all night.

March 10.—Ate light breakfast. Given morphin sulphate, grains 1½ (0.097 gram) at 8.30 A. M. Milk toast at noon. Comfortable. Sterile hypodermic at 12.30 P. M. Began to complain about 2 P. M., but was given another sterile hypodermic. No supper. Capsule containing calomel, grains 2½ (0.16 gram); powdered extract cascara, grains 2½ (0.16 gram); powdered ipecac, grams 1¼ (0.08 gram); strychnin sulphate, grain 1/16 (0.004 gram); atropin, grain 1/200 (0.00036 gram), given at 4, 6, 8 and 10 P. M.; morphin sulphate, grains 1½ (0.097 gram), at 7 P. M. Comfortable night. Slept six hours. One bowel movement during the night.

March 11.—Was given strychnin sulphate, grain 1/30 (0.002 gram), at 6.30 A. M. and magnesium sulphate, 1 ounce (31.10 grams). Light breakfast at 7 A. M. Strychnin sulphate, grain 1/30 (0.002 gram) at 8 and 8.30 A. M., and at 10.30 A. M. strychnin sulphate, grain 1/30 (0.00216 gram), and 2 ounces (59.2 c.c.) castor oil. Several copious bilious stools during forenoon. Was given sterile saline infusion, minims 10 (0.6 c.c.), every two hours by hypodermic during the day; 1,000 c.c. saline infusion at 2 P. M. Very comfortable day. Rather restless toward evening, and at 8 P. M., morphin sulphate, grain 1 (0.065 gram), was given. Slept nearly all night.

March 12.—Light breakfast. Morphin sulphate, grain ¾ (0.0486 gram), at 8 A. M. and sterile hypodermic every 2 hours during the day. Rather restless and uncomfortable toward evening, but not complaining much. No supper. Purgative capsules given at 4, 6, 8 and 10 P. M. Morphin sulphate, grain ¾ (0.0486 gram), at 8 P. M. Slept nearly all night. Bowels moved slightly at 4 A. M.

March 13.—Light breakfast. Strychnin sulphate, grain 1/30 (0.00216 gram), at 6.30 A. M. Same dose repeated at 8.30 A. M. and 2 ounces (62.2 grams) castor oil. No bowel movement. Strychnin sulphate, grain 1/30 (0.00216 gram), at 10.30 A. M., and bottle of citrate of magnesia. Nausea and vomiting at 11 A. M., and copious bilious stools frequently throughout the afternoon. Had 1,000 c.c. normal saline infusion at 2 P. M. Had sterile hypodermics every 3 hours during the day, and morphin sulphate, grain ½ (0.0324 grain), at 8 P. M. Complained several times during the day that his "shots" were not "holding" him. Slept quite well after his 8 P. M. hypodermic. Several stools during the night.

March 14.—Cross and irritable in morning. Asked to go home and had he not been committed, he probably would have gone, but since he was under the hospital control, his wishes were not granted. Was given hyoscin, grain 1/200 (0.00032 gram), at 9 A. M. and a dose of citrate of magnesia, only half a bottle being accepted. Had copious and free action of bowels at 9.30 and at 10.15 A. M. Was complaining of weakness and was beginning to sneeze and yawn. Hyoscin by hypodermic, grain 1/200 (0.00032 gram), at 12 M. Took a glass of hot milk. Bowels moved copiously and patient went to bed. Hyoscin, grain 1/200 (0.0032 gram), at 1 P. M. and at 2 P. M. The sneezing and yawning ceased, but patient was still restless and uncomfortable. Hyoscin at 3 P. M., grain 1/100 (0.00065 gram). Pupils dilated and face flushed. Throat dry and patient generally uncomfortable. Hot milk at 4 P. M. and grain 1/100 (0.00065 gram) hyoscin. At 5 P. M. patient was quieter but still uncomfortable. At 6 P. M. grain 1/100 (0.00065 gram) hyoscin; 6.30 P. M. patient was restless and mildly delirious, picking at bedclothes. Could be aroused and said he had some pain in his legs. Pupils widely dilated. Circulation good, although face flushed. Remained quiet until 9 P. M., when hyoscin, grain 1/70 (0.0008 gram), was given. Was delirious off and on till past midnight, but quiet and not complaining.

March 15.—Slept until 3 A. M. and awakened quite delirious. At 4 A. M. quiet, and slept for an hour. At 6 A. M. was lucid and complained of pains in his legs. He took a glass of water and his bowels moved. At 6.30 A. M. hyoscin, grain 1/200 (0.00032 gram), was given. Remained quite comfortable, though mildly delirious at times. At 10 A. M. commenced to ask for morphin and was given grain 1/100 (0.00065 gram) hyoscin. After this he was quiet but was mildly delirious and picked at the bed-clothes. At 1 P. M. took a glass of water and voided urine. Pulse of good quality, though only 65 per minute; temperature, 99° F. (37.2° C.); respiration, 24. Condition continued as above and no more hyoscin was given until 6 P. M., when the delirium had partly subsided. Said he would take a dose of morphin if he had it. Was given grain 1/75 (0.0008 gram) hyoscin. Was quiet for about fifteen minutes, and then became quite actively delirious and remained so for half an hour, when he lay quietly in bed and took several short naps. If left to himself he remained quiet, but in a semiconscious state from which he could be easily aroused. Remained in this condition until 10 P. M., when the delirium had nearly ceased. He complained only of weakness. Was given grains 1½ (0.097 gram) spartein sulphate. Became somewhat delirious again for about three hours but remained quietly in bed. Delirium ceased again and patient took several short naps.

March 16.—At 6.30 A. M. given bottle of citrate of magnesia; his mind was quite clear. Said he wanted no more morphin. Bowels moved twice, at 10 and 10.30 A. M. Asked for something to eat and had a glass of hot milk. Fell asleep till 1 P. M. Felt nauseated and vomited a large quantity of green fluid. Bowels moved again at 1.30 P. M. Patient slept until about 3 P. M. Took another glass of milk at 3.30 P. M. and retained same. No complaints except weakness. Had a hot bath and 15 grains (0.972 gram) trional and 15 grains (0.972 gram) sulphonal at 9 P. M. Slept about three hours and had a bowel movement. Slept again until 2.30 A. M.

March 17.—Patient was awake until 4 A. M., and then slept until 6 A. M., when he asked for nourishment. Had a cup of coffee and some dry toast, which he retained. Still complained of weakness but nothing else. Strychnin sulphate, grain 1/30 (0.002 gram), at 8 A. M. Fairly comfortable and no more medication till night. Had a glass of milk at 1 P. M. and said he would like something more. Had some milk toast. Hot milk and trional, grains 15 (0.972 gram), at 8 P. M. Slept from 9 P. M. until 1 A. M., and again until 3 A. M.

March 18.—Asked for coffee and toast. Bowels moved normally at 7.30 A. M. Temperature 99° F. (37.2° C.); pulse, 90; respiration, 18. Ate three meals and felt much better. Said he would not take morphin if it were offered.

At this stage the patient was upset by a letter from his wife who wrote that she needed his help and that one of his children was ill. He was told that the social service would help them, but he begged so piteously to go that his discharge was sent for, and next day he was permitted to leave the hospital in a rather weak condition, but not suffering and not wishing the drug. Subsequent history revealed that this man went back to the drug inside of twenty-four hours from sheer weakness.

This case illustrates how futile it is to attempt the treatment of these unfortunates unless conditions are such that they can have a prolonged convalescence in good surroundings.

CASE 5.—P. M., male, 31 years old, salesman; height 5 feet 8 inches, weight 135 pounds. Admitted as a voluntary case. Had used heroin, by sniffing, for four years and then heroin and cocain. Had used at least 10 grains (0.65 gram) of heroin a day and an occasional dose of cocain for the past year. Began as a "pleasure user," but has now become a slave to its use and says he uses it only because he is unable to live without it. Above average intelligence and of normal make-up.

This patient was anemic and undernourished. Skin was sallow. Bronchial catarrh with considerable secretion. Temperature 99.2° F. (37.3° C.); pulse, 80; respiration, 20. Mitral regurgitant murmur and slight cardiac hypertrophy. Good reserve power. Urine, normal. Tongue, coated and tremulous; breath, offensive. Very constipated. Poor appetite.

Feb. 15.—Admitted to narcotic ward at 1 P. M. Given usual preliminary bath and an enema. Sterile hypodermic at 2 P. M. and at 3 P. M. Began to get a little restless and uneasy. No supper. Purgative capsule at 4, 6, 8 and 10 P. M. Morphin sulphate, grains 2 (0.13 gram), at 8 P. M. Slept nearly all night.

Feb. 16.—Took strychnin sulphate, grain 1/30 (0.00216 gram), and Epsom salts, 1 ounce (31.10 grams), at 7 A. M. Light breakfast. No bowel movement. Strychnin sulphate, grain 1/30 (0.00216 gram), at 8 A. M. and again at 9 A. M. Bowels moved copiously several times before 11 A. M. Commenced to feel uneasy and asked for morphin. Sterile hypodermic given at 11 A. M. Bowels moved again at 11.15 A. M. Continued to complain, and morphin sulphate, grain 1 (0.065 gram), was given at 12 M. Was very comfortable and slept about two hours. Given 800 c.c. saline infusion at 2.30 P. M. No complaints. At 5 P. M. became restless and asked for morphin. Sterile hypodermic given. Took a light supper. Morphin sulphate, grain 1 (0.065 gram), at 8 P. M. Slept about six hours.

Feb. 17.—Strychnin sulphate, grain 1/30 (0.00216 gram), and a bottle of magnesium citrate at 7 A. M. Took a light breakfast. Bowels moved freely at 9 A. M. Asked for morphin, but was given sterile hypodermic at 9.30 A. M. Continued rather restless and complained that his legs ached. Sneezed occasionally. At 12 M. was given grain ¾ (0.0486 gram) morphin sulphate. Quiet through afternoon. No supper. Purgative capsules given at 4, 6, 8 and 10 P. M. Morphin, grain ¾ (0.0486 gram), at 8 P. M. Bowels moved once after midnight. Slept about five hours.

Feb. 18.—Refused breakfast except cup of cocoa. Was kept in bed. Given 2 ounces (59.2 c.c.) castor oil and strychnin sulphate, grain 1/30 (0.00216 gram), at 7.30 A. M. Bowels moved freely during the forenoon. Complained of weakness. Patient was given 1½ grains (0.097 gram) spartein sulphate at 10 A. M. Ate some milk and toast at 1 P. M. Spartein sulphate, grains 1½ (0.097 gram), at 1.30 P. M. Temperature 99° F. (37.2° C.); pulse, 84; respiration, 20. Was somewhat restless, and complained a little. Sterile hypodermic at 3 P. M. Continued a little restless and fussy. Spartein sulphate, grains 1½ (0.097 gram), at 8 P. M. Trional, grains 15 (0.972 gram), in hot milk at 8.30 P. M. Slept only four hours through the night, but toward morning was quiet and fairly comfortable. Bilious movement at 5 A. M.

Feb. 19.—Asked for breakfast and ate cereal and coffee. Was told he had been without morphin for over forty-eight hours. Said he could get along without any more.

This patient remained in the hospital over two weeks and was in very good health when discharged. He was sent to a farm in Vermont, where he remained three weeks. At present he is working in the city and is not using drugs as yet, and declares that nothing could tempt him to use it again under any circumstances. This patient did very well without using any hyoscin. Had his discomfort and reaction been too great following his last dose of morphin, the hyoscin would have been given him. This man was unusually determined, however, and would possibly have done a "cold turkey" if it had been necessary. (This latter is a term used by addicts to designate suffering the withdrawal phenomena without any treatment.) There are very few indeed who can accomplish this unless under restraint. The author knows of one patient who did so in his own home with morphin at his disposal. He later appeared for treatment and has remained well. Patients with such a determined desire as this offer very good prospects for permanent cure under good treatment.

CASE 6.—J. C., male, 27 years old, acrobat; height, 5 feet 8 inches; weight, 145 pounds. Voluntary case. Had used morphin by hypodermic for five years and now used approximately 12 grains (0.78 gram) a day. Usually takes 3 grains (0.195 gram) on arising; 2 grains (0.13 gram) at 11 A. M.; 2 grains (0.13 gram) in the middle of the afternoon; and 3 grains (0.195 gram) again at bedtime. Sometimes uses a little more and sometimes a little less than this. This patient did not present the usual picture of the drug addict, and only the pupillary contraction and sluggishness to light, together with the innumerable scars from hypodermics, would indicate his condition. He had always taken excellent care of himself. Only lately he had commenced to suffer from headaches, and his bowels were obstinately constipated.

Physically he presented normal heart, lungs and kidneys as far as examination could detect. Temperature, 99.6° F. (37.6° C.); pulse, 76; respiration, 18; pulse-pressure, 40.

April 3.—Admitted to narcotic ward at 10 A. M. Preliminary bath and enema given. Said this was about the time for his usual dose. Sterile hypodermic given. Was given nothing more until 3 P. M. when he commenced to complain and become very restless. Sterile hypodermic again given. Was quiet for an hour and then made quite a fuss, saying that the "shots were not holding him" and that he would like to have them raised. Another sterile hypodermic given at 4 P. M. Continued rather restless, but did not complain until 8 P. M., when grains 2½ (0.1624 gram) morphin sulphate was given. At 4, 6, 8, and 10 P. M. purgative capsules were given. Supper omitted. Slept about six hours.

April 4.—Strychnin sulphate, grain 1/30 (0.00216 gram), given at

7 A. M. and a dose of Epsom salts, 1 ounce (31.10 grams). No result at 9 A. M., when strychnin sulphate, grain 1/30 (0.00216 gram), was given and 2 ounces (59.2 c.c.) castor oil. Vomited the oil and a large amount of green fluid at 9.30 A. M. Was getting very restless and uneasy. Was given morphin, grains 2 (0.130 gram). Vomited again. Strychnin sulphate, grain 1/15 (0.00432 gram), given at 10 A. M. Still no bowel movement. Temperature 99° F. (37.2° C.); pulse, 90; respiration, 20. Strychnin sulphate, grain 1/15 (0.00432 gram), at 11 A. M. and one-half bottle of citrate of magnesia. No movement at 12 M., when strychnin sulphate, grain 1/15 (0.00432 gram), was repeated. At 12.15 P. M. bowels began to act. Large lumps of fecal matter were expelled and were followed by copious bilious stools throughout the afternoon. Had 8 stools up to 4 P. M. Felt decidedly better in every way. Sterile hypodermic at 4 P. M.

Became rather restless toward evening and was given 2 grains (0.130 gram) morphin sulphate. Slept nearly all night. Had two large bowel movements at 1 and 4 A. M.

April 5.—Strychnin sulphate, grain 1/30 (0.00216 gram), at 6.30 A. M. and again at 7.30 A. M. Bowels moved at 8 A. M. Took a cup of coffee and some toast. No more nausea. Sterile hypodermic at 10 A. M. Quite restless, but did not complain much, until 2 P. M. Light lunch at noon. At 2.30 P. M., 900 c.c. saline infusion. Commenced to get very uneasy and was given 1 grain (0.065 gram) morphin sulphate at 3.30 P. M. Slept two hours. No supper. Purgative capsules at 4, 6, 8 and 10 P. M., also morphin sulphate, grain ¾ (0.0486 gram), at 10 P. M. Had five stools during the night and slept only about three hours.

April 6.—Quite restless and uneasy on arising. No breakfast. Asked for morphin at 9 A. M. and was given sterile hypodermic. Complained of pains in his legs and became very irritable and nasty to the nurses. Was given hyoscin, grain 1/200 (0.00032 gram), at 10 A. M., and also at 11 A. M. Was quieter but still complained of pains in his legs. Was given hyoscin, 1/100 grain (0.00065 gram), at 12 M. Took a glass of milk and slept about an hour. Sterile hypodermic at 1 P. M. Began to complain and asked for morphin. Hyoscin, grain 1/75 (0.00086 gram), given at 1.30 P. M. and grain 1/100 (0.00065 gram) at 2.30 P. M. A large bowel movement at 3 P. M. Hyoscin, grain 1/100 (0.00065 gram), at 3.30 P. M. Temperature, 99° F. (37.2° C.); pulse, 68; respiration, 24. Face, flushed and perspiring profusely. Hyoscin, grain 1/100 (0.00065 gram), at 4.30 P. M. Still perspiring, and expectorating a white, foamy fluid. Became quiet. Cup of milk at 6 P. M. Hyoscin, grain 1/100 (0.00065 gram), at 8 P. M. and again at 10 P. M. and 1 A. M. Restless and complaining until 2 A. M., when he had hyoscin, grain 1/75 (0.00086 gram). Became quiet and slept at intervals toward morning.

April 7.—Given bottle citrate of magnesia at 6.30 A. M. Asked for breakfast at 8 A. M. Said he wanted no more hypodermics. Bowels moved at 9 and 9.30 A. M. Complained of feeling a little weak, but otherwise very well. Given spartein sulphate, grains 2 (0.130 gram), by mouth, at 10 A. M. Ate a little dinner. Spartein sulphate, grains 2

(0.130 gram), given by mouth at 2 P. M. Bowels moved copiously at 2.15 P. M. Given 800 c.c. normal saline infusion at 3 P. M. Slept until 5 P. M. Trional, grains 15 (0.972 gram); sulphonal, grains 15 (0.972 gram), in hot milk at 8 P. M. Slept at intervals during night. Somewhat restless, but not complaining. Did not ask for hypodermic.

April 8.—Was rather drowsy all day. Had two good bowel movements during morning. Took some milk toast for dinner and an eggnogg at 3 P. M. Complained of feeling a little weak during the afternoon and was given spartein sulphate, grains 2 (0.130 gram), by mouth. Had glass of milk and some toast at 6 P. M. At 8 P. M. 15 grains trional (0.972 gram). Slept till midnight and from 2 to 4 A. M.

April 9.—Asked for a full breakfast and said he felt much better. No desire for morphin. Up and about the ward for greater part of the day. Temperature, 98.4° F. (36.8° C.); pulse, 76; respiration, 20; blood-pressure, systolic, 130; diastolic, 100; pulse-pressure, 30. Had 900 c.c. normal saline infusion at 3.30 P. M. Two normal bowel movements during day. Ate light supper. Slept about 8 hours.

This patient remained in the hospital six more days and was discharged in excellent condition. Was seen a month later, but not again after that. He had not returned to the habit at that time.

This case illustrates how much larger doses of strychnin are required to bring about the proper motor reaction of the bowels in some addicts than in others. Some cases will require even more than was given to this patient, especially when the addiction to morphin has been in larger doses and of longer duration. Had the patient sufficient time to spend in the hospital, it is quite possible that this case could have been treated without hyoscin.

CASE 7.—P. A., male, 42 years old; weight, 140 pounds; height, 5 feet 11 inches. Had used morphin for fifteen years continuously. Commenced habit by smoking opium. When seen used approximately 20 grains (1.3 grams) a day by hypodermic.

Patient greatly undernourished. Had lost 45 pounds during the past three years; his muscles were soft and flabby; tongue, coated and breath offensive. Very constipated. Unable to make any prolonged effort without great fatigue and obliged to resort to hypodermic injection before he undertakes anything requiring even slight exercise. Temperature 99° F. (37.2° C.); pulse, 80-90 per minute; blood-pressure appeared to be low, but was actually 190 systolic. Respiration, 22. Slight bronchial catarrh. No cardiac murmurs and no hypertrophy, but sounds were all of poor quality. Kidneys were apparently normal. Fine tremors of extended fingers.

Patient admitted as a voluntary case. Had taken 3 grains (0.195 gram) just prior to coming to the hospital. Given preliminary bath and an enema. Entered ward at 4 P. M. and stated that he could remain only ten days. No supper. On admission was given strychnin sulphate, 1/15 grain (0.00432 gram), and also capsule containing the purgatives before mentioned. Capsules were repeated at 6, 8 and 10 P. M. Slept five hours during the night. He commenced to call for morphin toward morning.

April 4.—Strychnin sulphate, grain 1/30 (0.00216 gram), at 6 A. M., and at 7 A. M. the same dose was repeated, and also 2 ounces (59.2 c.c.) of castor oil. Became somewhat nauseated by 8 A. M. and commenced to get restless and called for his drug. Bowels had not moved. Given strychnin sulphate, grain 1/15 (0.00432 gram), at 9 A. M. and a bottle of citrate of magnesium. Had a profuse, semifluid stool, followed by a copious, greenish evacuation at 10 A. M. Was given morphin sulphate, grains 2 (0.130 gram), at 10.30 A. M. Between 11 A. M. and 12 M., patient had two more watery movements. Took a light lunch. Fairly comfortable during the afternoon. Had morphin sulphate, grains 2 (0.130 gram), at 2 P. M. and again at 6 P. M. Had a light supper. Spent a comfortable night.

April 5.—Strychnin sulphate, grain 1/30 (0.00216 gram), at 6 A. M. Morphin sulphate, grains 2 (0.13 gram), at 8 P. M. Comfortable. Morphin sulphate, grains 1½ (0.097 gram), at 11 A. M. Up and about ward and out on porch. Ate lunch and took an egg-nogg at 3 P. M. Had morphin sulphate, grains 1½ (0.097 gram), at 3 P. M. No supper. At 4, 6 and 10 P. M. had the purgative capsules. Slept fairly well until about 2 A. M., and from then on was restless, but not complaining.

April 6.—At 6.30 A. M. had strychnin sulphate, grain 1/15 (0.00432 gram), and 1 ounce (31.10 grams) magnesium sulphate. Strychnin sulphate, grain 1/30 (0.00216 gram), at 7.30 A. M., and at 8.30 A. M. the same dose and also 2 ounces (59.2 c.c.) of castor oil. Bowels commenced to move very freely at 9.30 A. M. Asked for morphin and was given grain 1 (0.065 gram) at 10 A. M. Had four copious bowel movements up to noon. Took a light lunch. Fairly comfortable. Pulse, systolic, 78; blood-pressure, 150. At 2 P. M. was given morphin, grain 1 (0.065 gram), and at 3 P. M. a saline infusion of 900 c.c. was made into the vein. Color decidedly improved. Said he felt more like himself than he had in years. At 6 P. M. took light supper, and had strychnin sulphate, grain 1/30 (0.00216 gram). Began to get rather restless by 8 P. M. and was given 1 grain (0.065 gram) morphin. Slept from 9 P. M. until 1 A. M. and from 2 to 5 A. M.

April 6.—At 6. A. M. had strychnin sulphate, grain 1/30 (0.00216 gram), and at 6.30 A. M. a bottle of magnesium citrate. Bowels moved copiously at 8 A. M. Was quite restless and requested a hypodermic. Was given hyoscin, grain 1/100 (0.00065 gram), at 8.30 A. M. and again at 9.30 A. M. Temperature, 98.6° F. (37° C.); pulse, 70; respiration, 18; pulse-pressure, 30. Given 1,000 c.c. normal saline infusion into external jugular vein (administered in this manner when veins in arms are difficult to deal with for any reason). Slept for two hours, and awakened sweating rather profusely, and asked for drug. At 11.30 A. M. patient was given hyoscin, grain 1/100 (0.00065 gram), and same dose was repeated at 12 M. Asked for a drink of milk which was given. Rather restless for half an hour and then fell asleep again. Temperature, 99° F. (37.2° C.); pulse, 80; respiration, 20; pulse-pressure, 25 at 1 P. M., when patient awakened. Was given hyoscin, grain 1/100

(0.00065 gram). Sweating, and face flushed. Complained of dryness of throat and asked for a drink of water, which was given. Became mildly delirious; picked at clothes, but remained quietly in bed. Could arouse him completely and then he would lapse into a semistuporous state. Remained in this condition until 4 P. M., when he began to complain of pains in his legs. Urinated. Had hyoscin, grain 1/100 (0.00065 gram), at 4.30 P. M. and again at 5 P. M. Continued in a semistuporous state, muttering mildly to himself and occasionally picking at the bed-clothes. Slept occasionally. Was given hyoscin, grain 1/100 (0.00065 gram), at 7 P. M. Slept until 9 P. M., when he awakened and his mind was quite clear. Complained of feeling weak but otherwise well. Hyoscin, grain 1/100 (0.00065 gram), was given. Slept until 11.30 P. M., when he awakened and voided urine, and asked for water. Hyoscin, grain 1/100 (0.00065 gram), given. Soon lapsed into semiconscious state, napping at intervals. Muttered to himself occasionally. Remained this way until 2 A. M., when hyoscin, grain 1/100 (0.00065 gram), was given. About an hour after this, patient's mind commenced to wander slightly, but he remained quiet and slept at intervals until 5 A. M.

April 7.—Mind was entirely clear at 5 A. M. Was given a bottle of magnesium citrate. Bowels moved at 6.15 A. M. Asked for something to eat and was allowed a light breakfast. Bowels moved again at 7 A. M. Complained of feeling weak, but otherwise felt well. Given hyoscin, grain 1/75 (0.00086 gram). Patient slept two hours. Spartein sulphate, grains 2 (0.13 gram), by mouth at 9 A. M. and repeated at 11 A. M. Said he felt very much stronger and did not wish more hypodermics. Asked for something to eat and was given milk and toast. Drank an egg-nogg at 1 P. M. Was a little restless during the afternoon, but did not ask for hypodermics. Drank a glass of milk at 6 P. M., and at 8 P. M. had a warm bath. At 8.30 P. M., a glass of hot milk and trional, grains 15 (0.972 gram), and sulphonal, grains 15 (0.972 gram), were given. Slept from 9 until 1 P. M. and from 2 to 5 A. M., when he had a bottle of magnesium citrate. Said he felt very much better. Bowels moved at 6 A. M.

April 8.—At 6 A. M. had spartein sulphate, grains 2 (0.130 gram), by mouth. Had breakfast at 7 A. M. and patient was allowed to be up. Remained up all day. Complained slightly of pain in the knees and was given aspirin, grains 10 (0.650 gram), at 3 P. M. and again at 6 P. M. Slept six hours without medication.

This patient remained in the hospital four more days. Although he stated he had not felt so well in years and that he had no desire for his drugs, his subsequent history might have been different had he been able to remain under treatment for a few months in some good sanitarium.

At the end of a month he returned and reported that he had been using the drug for a week. Upon careful questioning the facts were brought out which led to the relapse. Contrary to advice given him on leaving, he had eaten to great excess with no restrictions on anything. By the end of the second week his bowels became constipated and he commenced to experience headache and general weakness. He consulted a physician who told him he was suffering for the want of his drug, and the patient was only too ready to believe this.

Unfortunately the above history is altogether too frequent. The author has had knowledge of hundreds of just such cases. Any symptom which may happen to arise in one who has once been addicted to narcotic drugs, no matter from what source or how long after a treatment for addiction, is promptly considered to have some close connection with this former habit. Recalling how quickly a hypodermic relieved them of discomfort at one time, patients are inclined to resort to it again. It is most discouraging from a prophylactic standpoint when this same idea is also fostered by physicians. The author has seen 2 cases of gonorrheal arthritis for which morphin was prescribed to former addicts under the impression that it was a withdrawal symptom. The patient knew that such was the case. The author has seen dozens of cases of intestinal toxemia, arising from overeating and neglect of the bowels, for which drug has been advised under the assumption that all the trouble was due to their former habit and that nothing but their drug would relieve them.

During Convalescence the Diet Is Very Important. It should be simple, well-balanced, and never in greater quantities than required. The return of the appetite in addicts who have been properly treated is likely to cause them to overindulge and abuse themselves, so that the appetite is not a good guide to follow at this time. **Coffee, tea, alcohol, and excess of proteids are to be absolutely forbidden** for several months, if the best results are to be looked for.

Prognosis.—This depends upon many factors. First and foremost, it depends upon the *personality of the addict* himself. Those who have acquired the habit through their own volition offer a poorer chance of permanent recovery than those who were so unfortunate as to become the victims through outside agencies. Among the former class, it is usually only after years of addiction have made them veritable slaves that there is any impulse to give up the habit.

Naturally, that class of addicts who originally sought refuge in drugs because of their inability to sublimate along higher levels are likely to again revert to the same measures. Such cases remain free from the drug, after appropriate treatment, for any time from a few weeks to a few years and then return again to their addiction. They acquire the habit anew again and again. For such cases, the only absolute hope of permanent freedom from drugs is the total inability to get them. But even among this class there are hopes for permanent results in some cases. Among the younger addicts of this class a permanent cure can rarely be hoped for because they often have no real desire to overcome the habit permanently. If a true desire is present, however, and correct treatment both of a physical and psychotherapeutic nature is instituted, relapse is not so likely.

That class of unfortunates, however, which has been the victim of drugs through circumstances independent of their own volition offer very good material for cure. These have never been willing slaves of the drug, and have always looked forward to their liberty. When they are once again in good physical condition, in many cases death itself would be welcome rather than a return to the habit. However, even these patients, if any painful illness ever overtakes them, are again likely to resort to drugs.

Other factors which enter into the prognosis are the *age of the patient* and the *length of time of the addiction.* One would naturally think that a young healthy person who has been an addict for only a few months or years would offer the better material for a permanent result; the opposite, however, is usually the case. These young addicts still find satisfaction in the use of the drug. They have not as yet come to the point where they see the real harm in the vice and will not admit it has done them any harm. They seek a cure, and remain away from the drug for a certain period, and then tamper with it until a habit is again established. They have not yet been taught their lesson. Prolonged suffering or some other intense experience is necessary to make them see the light.

On the other hand, the author has seen cases of many years' standing in which the patients show no tendency to relapse, but these were invariably stable individuals of normal intelligence capacity.

For a person who has the desire to be permanently free from addiction, once he has been treated thoroughly, it is necessary to abstain from alcohol and drugs of all sorts, unless under the special direction of a physician who is aware of his former habit and therefore thoroughly comprehends the situation of the patient. Everything possible must be done to keep up a healthy physical and mental condition. Habits of right living must be inculcated and excesses of all kinds avoided.

Good results can never be expected if the habit is looked upon as a vice. It is true that in many cases it is a vice, but in a great many more the habit is accidentally acquired, and in the vast majority of cases it arises through the inability to meet the stern realities of life, so that it is no more a vice than a neurosis or psychosis would be. In all cases, once the drug is taken for a few weeks a real physical disease arises—a toxemia. Thus we see that there are two elements in the causation—one the personality, and the other arising directly through physical causes. Both these factors must be considered in the treatment and prognosis of any such cases.

Pathology.—There is no specific structural pathology which has been demonstrated in this disease. One would hardly wish to conclude from this, however, that there is no pathology. Experience gained from the observation of many thousands of cases has led the author to regard the disease as a *mixed toxemia.*

The reduced activity of all the secretive and excretive glands which is brought about through continued use of the drug results in an accumulation of waste products in the body in addition to the drugs themselves. The eliminating organs never have a full chance to carry on their work. When the drug is stopped entirely, all the eliminative organs take on a great activity, and diarrhea, vomiting, sweating, etc., take place.

From the picture one can hardly escape the conclusion that the body has been simply saturated with toxins of both metabolic and intestinal origin. Experiments have been made, and conclusions drawn, regarding certain antibodies which appear in the blood of morphinists. There is much work left to be done, however, before these can be regarded as conclusive. Treatment based upon this pathology yields better results than any other and only helps to confirm one in the opinion that it is a toxemia. All the secondary changes which were described under the Symptomatology of the disease are dependent upon these toxins.

In considering the physical basis of the disease, however, one should not lose sight of the psychopathology, because if one does so, one will meet with many disappointments. The various conflicts and difficulties which are the foundation of addictions in many cases must be delved into and unearthed, and higher, more noble adjustments substituted.

COCAIN ADDICTION

Etiology.—The use of this drug is most often taken up as a pure dissipation. The characteristic withdrawal phenomena which are found in addicts of opium or one of its derivatives are not observed in the cocain habitué. Its continued use, however, is more degrading than that of opium and its derivatives, and leads to more crime and danger.

In the northern states the addiction to cocain alone is relatively uncommon. In this locality, it is most often taken up by those addicted to morphin and heroin when they are no longer able to gain pleasurable results from the latter, and is taken in conjunction with these drugs. In the southern states, and chiefly among the negroes, it is used much more extensively. In the South American countries, especially Brazil, it is gaining quite a foothold at the present time.

The fact that it can be taken without any marked withdrawal symptoms, permits of its use intermittently, just as alcohol is often used, even under similar circumstances. Consequently the habit is not prolonged because of abstinence phenomena, but rather because of the memory of its former effects, which drives the cocainist with irresistible passion to the use of the drug.

Symptomatology.—Physiological Effects.—The effects of cocain are rather fleeting and more and more of it is finally required to obtain the desired results. Marked cachectic conditions and emaciation follow chronic addiction. The muscles become soft and flabby, and the vessels lose their tone. Trophic disturbances often occur in the skin and nails, and crops of boils are sometimes found. Necrosis of the cartilaginous portion of the nasal septum is not infrequent in cocain sniffers. The sexual functions become impaired and finally lost.

Psychological Effects.—In the psychic realm, the effects of chronic cocain-poisoning are pronounced and striking. When taken in small doses, cocain at first exerts a stimulating influence upon the sensory elements of the nervous system. A feeling of euphoria or well-being is noted and the mentality appears more active. The libido is increased. In large doses, however, a paralyzing effect is obtained, thought is retarded, depression occurs and insomnia becomes more marked. A state of restlessness and apprehension ensues. The mentality becomes blunted and forgetfulness and absentmindedness are added. The general moral tone becomes lessened to a remarkable degree, and all interest in home and vocation is lost. Lying and stealing become common; slovenly and careless personal habits become the rule. Addicts become quarrelsome and irritable and maintain a suspicious attitude toward their relatives and former friends, thus resembling certain chronic alcoholics.

With sufficient doses of the drug, a veritable psychosis may finally supervene, in which an hallucinatory delusional state exists. The false sense perceptions are chiefly of a tactile or visual nature; very often both are combined. Hallucinations of hearing also occur, but are not so characteristic or common. The hallucinations are multiform and fleeting: Bugs, worms and insects are felt crawling on the skin; bits of glass, needles and pins, acid, etc., are also felt and seen. Various obnoxious vapors and gases are scented. Men are seen pointing guns at them, and they are being watched and persecuted. Filthy names are called out to them, and obscene pictures are thrust in their faces. Delusions of jealousy develop, much as in alcoholics. This hallucinatory state may finally, after a long sleep, end in recovery. Collapses, convulsive seizures and death, however, often take place.

Treatment.—This will be considered under two headings: first, in those who use the drug alone, and secondly, in those who use it in combination with morphin or heroin. When it is taken alone, the only physical treatment necessary is a **thorough catharsis.** The **patient** should be **placed in bed and isolated.** He will be likely to sleep for 24 hours or even longer without interruption. He will then awaken and be ready for his dose if it be forthcoming. None will be required in the treatment, however, as there are scarcely any withdrawal symptoms. Everything should be done to **build up the patient's general bodily and mental health,** and this is best accomplished in a sanitarium or like institution where the patient can be kept under such treatment for months. The longer he is kept under such treatment, the better the likelihood of a cure. Less than six months will hardly do, and twelve months is none too long.

In the cases in which cocain is combined with morphin or heroin, it is best to put them through the same eliminative treatment that is recommended for morphinists, but to withdraw the cocain at once, and the morphin rather rapidly.

Prognosis.—The prospect for a complete cure for this habit is not particularly promising in a majority of the cases. The type of persons who use this drug are often of an inferior make-up, and amongst them are to be found many borderline mental cases. The worst of these should be permanently segregated, inasmuch as they are a menace to society under any condition, both with and without the drugs. They will continue to breed vice and crime, and will continue to propagate their kind as long as they are allowed the freedom of society. Sequestration in community villages, under state supervision, is the proper remedy for these unfortunates.

In the cases of cocain habit in the higher types in which there are no primary defects of intelligence or affectivity, and in which no permanent deterioration has taken place, the outlook is, of course, better. Even here, however, many months of treatment under good conditions are necessary in order to be of any lasting benefit. A year is none too long to insure success in these cases. No amount of treatment of any nature will obliterate in the patient the memory of the sensation he experienced with the drug, and whatever induced him to use the drug in the first place may cause him to resort to it again as a dissipation.

PARALDEHYD HABIT

While it may be truly stated that the addiction to this drug is not common at present, it does, however, occur and, during the past year alone, several patients have been under the author's personal observation. All but one of these had been heavy drinkers who had entirely given up the habit, and the exception took the drug habitually between alcoholic sprees. It is rather doubtful whether the addiction to this drug will ever become a serious social menace, as its hot, pungent taste and highly disagreeable odor, which cannot be obliterated, render it highly obnoxious to most individuals. However, it is not to be forgotten that total prohibition of alcohol is likely to breed vice in other directions, and various drugs of a sedative and anodyne nature may be substituted in many cases.

Symptomatology.—The continued use of this drug over a period of years may result in a peculiar form of delirium, which is quite characteristic and in its nature resembles somewhat a bromid delirium, but differs from an alcoholic delirium, in that the typical apprehensive state is wanting in a great measure, the coarse tremors are not present, while the content of the delirium is more dreamlike and less terrifying. Then, too, the patient may be momentarily aroused and becomes for the time quite oriented and recognizes those about him; but when his attention weakens, he at once lapses into his previous condition and is very busy with his former occupation, and holds conversations with his old associates.

The following history illustrates one of these cases:

The patient, a male, aged forty-six, had, up to a year and a half before admission to the hospital, been a heavy and steady whiskey drinker, though he never became drunk, and had never had delirium tremens. About the time he gave up his alcoholic habit he commenced to take a nightly dose of about 2 drams of paraldehyd. This he gradually increased to over half an ounce, and occasionally indulged in small doses during the daytime.

On the day of his admission he walked out of an open window at his house and was taken to the hospital with an injury to his leg. He was in an active delirium, talking constantly about some construction work in which he thought he was engaged, did not appear frightened and could be easily aroused, in which moments he would recognize the nurses and doctors, and talk quite rationally. He remained in this state for about five days before he became entirely himself. Then he gave the history as given, and stated that for the past few days prior to the onset of his sickness, he had been suffering with severe headache and had indulged more frequently than ever in the paraldehyd.

Treatment.—In the treatment, it is only necessary to **isolate the patient,** and endeavor to **produce sleep through prolonged baths.** There are no characteristic withdrawal phenomena. The patient will resort to this or some other drug in the future if he is of a subnormal or unstable type. Otherwise, following the removal of the paraldehyd, if he is **placed in a suitable institution with outdoor exercise and good general treatment,** his chances for overcoming the habit are very good. Where chronic alcoholism is the basis of the trouble, he should be treated along the usual lines.

BROMID HABIT

That the continued use of the bromids may lead to a habit in the same sense that the continued use of opium, morphin or heroin do, is certainly not the case. There are, however, not a few individuals, who, because of some underlying nervous disorder, resort daily to bromids for relief, and soon become so accustomed to their use that a habit is established.

Symptomatology.—The bromin is accumulated in the system, displacing the chlorin from its compounds in the fluids and cells, and leads in time to disturbances in nutrition, in the skin and in the nervous system. *In the skin* there appears the rather characteristic bromid rash or acne. Large pustules without any inflammatory area may appear. The contained pus shows the test for bromid. Considerable *loss of weight* often follows, associated with a *catarrhal condition of the alimentary and respiratory tracts.*

In the *central nervous system* the very profound symptoms often appear even in the absence of the above, as well as often associated with them. The general excitability of the nervous system is greatly lowered. Pains in the head and legs and weakening of the superficial reflexes may appear. In some cases the knee-jerks may totally disappear. The speech becomes mumbling and the gait tottering. In the psychic field grave symptoms may supervene. Attention and retention become greatly impaired as well as the judgment and the association of ideas. A rather typical delirium often develops in some cases, which in a measure reminds one of the Korsakoff syndrome. A calm and composed bearing is often maintained with a tendency to fabrication and confabulation. The perspiration, tremors and apprehensive state of the characteristic alcoholic delirium are lacking.

Treatment.—The treatment of such a habit consists of the **removal of the underlying physical or mental state,** together with elimination of the bromids. The administration of **saline infusion,** 1,000 c.c. daily for several days, will soon accomplish the last, particularly if salt in considerable quantities is given with the diet.

CHLORALISM

Addiction to chloral is even less common than the bromid habit. However, it does occur occasionally, and consequently it is to be borne in mind. Its victims are usually neurotics who have taken the drug for insomnia, either on a physician's prescription or through a druggist's recommendation. The patient soon begins to depend upon his nightly dose for sleep and is unable to get along without it.

Symptomatology.—It acts as a depressant to the circulatory system and in time leads to severe symptoms. After several weeks or months of its use, the patient develops signs of cardiac weakness, such as dyspnea, vertigo, etc., and becomes easily fatigued. Psychic symptoms, such as depression and forgetfulness, appear and insomnia becomes more and more pronounced.

Treatment.—As in all addictions, the treatment should first be directed toward the **correction of any underlying physical defects.**

The **daily dosage** must be **gradually decreased** and during this period it may be necessary to substitute some other drug, such as trional, sulphonal, etc. Great care must be emphasized in using such substitutes, however, as another habit, equally as bad, may be induced. **Alcohol and morphin** particularly **must be avoided.**

During the early part of the treatment and preferably for a long time following, **isolation** is absolutely necessary. For a time **rest** in bed is indicated, accompanied by **forced feeding, massage, hydrotherapy and general tonic treatment.** Spartein sulphate, digitalis and other cardiac supporters are often necessary during the withdrawal period. Such cases rarely do well as ambulatory patients, so it is always advisable to place them in a properly equipped hospital or sanitarium.

ADDICTION TO OTHER DRUGS

The limits of this work will only permit the mention of certain other drugs which often lead to habits, especially in neurotic individuals.

Veronal, particularly, is often indulged in to the extent that it becomes a habit and a stuporous, lethargic and drowsy condition results, which requires treatment. *Trional, sulphonal, ether, chloroform, antipyrin, phenacetin, cannabis indica, chloralamid, asperin, bromo-seltzer, bromidia* and combinations of these various drugs may also become dangerous in certain constitutions. These are usually indulged in for the relief of insomnia or some other such condition, and treatment should be directed toward the relief of such underlying nervous states.

CHAPTER III

LEAD-POISONING

(*Saturnism, Plumbism*)

By Tasker Howard, M.D.

Acute lead-poisoning, p. 59—Chronic lead-poisoning, p. 59:—Etiology, p. 59:—Predisposing factors, p. 59; Toxicity of various salts of lead, p. 62; Modes of entering the system, p. 62—Symptomatology, p. 62—Diagnosis, p. 67:—Differential diagnosis, p. 67—Association with other diseases, p. 68—Treatment, p. 68:—Prophylaxis, p. 68; General management, p. 68; Medicinal treatment, p. 69; Symptomatic treatment, p. 70—Prognosis, p. 71—Pathology, p. 72—Historical summary, p. 73.

ACUTE LEAD-POISONING

Acute lead-poisoning is very rare, but may occur as the result of the ingestion of a large dose of some lead salt. The *symptoms* are those of an acute gastro-enteritis: epigastric pain, nausea and vomiting, and diarrhea. Rarely is enough of the metal absorbed to bring about the systemic effects of lead which will be considered under chronic poisoning.

The *treatment* for acute poisoning consists of prompt **lavage,** whether or not the patient has vomited, and the administration of **albumin water** or **milk.** A **purgative** to hasten the evacuation of the poison is indicated, and **magnesium sulphate** has the advantage of combining to form lead sulphate, which is not so readily soluble in the gastric juice as are some of the other salts. In the intestine lead sulphate is not dissolved. The patient will demand the symptomatic care ordinarily required in the treatment of gastro-enteritis.

CHRONIC LEAD-POISONING

Etiology.—Chronic lead-poisoning is the most widely recognized and widely distributed occupational disease. Its occurrence as the result of the absorption of lead salts accidentally from sources other than industrial is, however, not at all uncommon. Ingestion of the metal from one source or another is, of course, the one cause of this disease, but a number of factors must be considered as bearing upon the development of the symptoms.

Predisposing Factors.—*Age.*—The young are peculiarly susceptible to the influence of lead, babies and children reacting to proportionately smaller doses than adults. It is probably true that young adults are more susceptible than their elders. It has been stated that the middle-aged are more frequently attacked, and there is no doubt that a majority of the patients applying for treatment for chronic lead-poisoning are well past their youth, but these patients have in the majority of instances been long exposed to lead and have gradually been developing symptoms which have finally sent them to a physician.

Race.—Negroes are said to be more susceptible to lead-poisoning than are whites. Edsall and Hamilton have both found the negro to be particularly prone to encephalopathies.

Sex.—In the United States the number of women employed in industries which predispose to lead-poisoning is proportionately much smaller than the number of men, and we consequently see much less of the disease in women. Oliver, however, emphasizes the fact that women are much more readily affected than men. Alice Hamilton found the incidence to be 1 to 7 among women and 1 to 12 or 13 among men in the pottery and allied industries in the United States. It is stated that hysteria and cerebral involvement are proportionately more common among women.

Season.—Season probably exerts no particular influence upon the incidence of lead-poisoning, except as it affects the activities of the various trades which involve exposure to lead. Thompson points out that in the winter indoor workmen are less apt to keep their doors and windows open and are consequently more exposed to the action of dust and fumes. Some authors report that attacks are more common in summer than in winter.

Heredity.—There is some evidence to show that certain families are more susceptible to the influence of lead than others. Women who have lead-poisoning are very apt to abort or give birth to premature infants. The tissues of such infants have been shown to contain larger amounts of lead than is normal. The wives of lead workers are also prone to abort. In a statistical study of 400 painters, Harris found that 20 per cent. of the pregnancies in the case of the wives of men suffering from active lead-poisoning ended in abortion, and 8.5 per cent. of the pregnancies in the wives of unaffected painters terminated in this way. The children of lead subjects, whether the mother or the father is affected, are apt to be underweight and delicate. This results, in the case of maternal involvement, from the anemia and poor general nutrition of the mother, as well as from the effects of the lead itself upon the embryo. Where the mother is sound and the father affected by lead, the effect upon the child is due to the blastophoric influence of the disease upon the spermatozoa. Weller has reproduced these phenomena in guinea pigs. An examination of the testes showed no evident histological changes, except in pigs in which he had produced sterility. In these pigs atrophic aspermatogenesis was demonstrated.

Individual Susceptibility.—Individual susceptibility to the effects of lead varies greatly. Hamilton reports one case of colic and palsy resulting after three days' exposure in a white lead factory. On the other hand, certain workers can continue to expose themselves for years without any symptoms.

Chronic Alcoholism.—Most observers agree that heavy drinkers are much more prone to plumbism than are the temperate. It is reasonable that this should be so, aside from the general debilitating effect of alcoholism, because of the hyperacidity which is primarily induced, the chlorid compound in the stomach presenting the most soluble and dangerous of the lead salts.

Personal Habits.—Personal cleanliness is a definite safeguard against lead-poisoning, and the reverse holds true, that filth and dirty habits predispose to the disease. In many trades the danger of lead-poisoning lies in the possibility of swallowing lead salts with the food, and the absolute necessity of carefully cleansing the hands, face and mustache before eating is quite evident. The care of the clothes, the mouth, the hair, are all important. Aside from these specific precautions, the ordinary dictates of hygiene, such as proper diet, fresh air, sleep, exercise, etc., are important in establishing resistance to this as to other diseases. The predisposing influence of squalid living conditions is well illustrated by the fact that lead-poisoning was found to be three times as prevalent among the workers in the potteries at Zanesville, where the prevailing wages were from $1.25 to $1.65 a day, as it was at East Liverpool, where the workers received from $2.50 to $5.00 a day. (Hamilton.)

Occupation.—There are over one hundred and fifty trades which expose the workman to lead-poisoning. Among the most important of these are lead-mining and smelting, making of alloys, the manufacture of white or red lead and their use in the making and handling of paints, type-making and setting, plumbing, glazing china and porcelain, preparation of certain rubber goods, leather finishing and harness-making, file-making, manufacture of storage batteries, weighting silk, etc. So diverse and numerous are the ways in which lead-poisoning may be acquired that its possibility should always be borne in mind, and when symptoms are at all suggestive the character of the work should be inquired into in detail. Sailors are not infrequently victims because of the paint they handle. A number of the author's Long Island patients were sailors. Dressmakers sometimes acquire the disease from biting off the ends of silk thread which has been weighted with lead. Laundresses have contracted it from washing the clothes of painters and workers in lead.

Other Sources of Lead-poisoning.—Drinking water which has passed through new lead pipes, before a protective coating of lead carbonate has been deposited, is a not uncommon source of lead-poisoning. Beer, ale, cider and sour wines are sometimes contaminated by lead pipes or fixtures, and have been responsible for some considerable epidemics of plumbism. Hair dyes and cosmetics are sometimes the source of poisoning. In rare cases lead administered medicinally has caused symptoms. The retention of a lead bullet is said to have been responsible for symptoms, but this danger cannot be more than extremely remote.

TOXICITY OF VARIOUS SALTS OF LEAD.—Lead is taken into the system in various forms. The metal itself is rarely ingested as such. The surface of lead is usually more or less oxidized, and this oxid rubs off on the worker's hands and is a source of poisoning. The toxicity of the different salts depends largely upon their solubility. Lead sulphid is the only salt which is insoluble in the gastric juice. It was once supposed that the sulphate was insoluble in the stomach, but it has been shown that the peptone in the gastric juice renders this salt soluble in the hydrochloric acid. The chlorid, oxid, chromate, acetate, are all soluble in the stomach. The physical characteristic of a salt is a very important factor in its toxicity. The oxids are light and are readily blown about, so that they are frequently inhaled and swallowed. The same is true of the basic carbonate, chromate and sulphate. The fumes of the suboxid, formed and volatilized on the surface of the molten lead, is a source of much poisoning. White lead (basic carbonate) is heavier but is so widely used that it is probably responsible for more cases of poisoning than any other salt. Lead acetate (litharge) is also heavy and somewhat sticky.

MODES OF ENTERING THE SYSTEM.—By far the commonest route by which lead enters the system is through the alimentary tract. Painters and workers in various lead salts soil their hands with the product and may carelessly convey it to the mouth with their food or with a pipe, cigar or chewing tobacco. Quite as commonly their mouths become contaminated with lead dust, which they swallow with the saliva. Certain of the dusty salts are inhaled, and are probably absorbed to some extent by the mucous membrane of the respiratory tract. It has been claimed by good authorities that toxic doses of lead can be absorbed through the skin, but this seems improbable, as Hamilton has pointed out that, in some forms of pottery-making and glazing, workers have their arms immersed to the shoulders in compounds containing from 5 to 20 per cent. of lead, with no higher incidence of poisoning than in the case of other workmen not exposed in this manner.

Symptomatology.—PERIOD OF DEVELOPMENT.—The major manifestations of lead-poisoning may be summarized as lead colic, peripheral neuritis and encephalopathies. The period from the beginning of the exposure to lead until the development of these symptoms varies greatly with the susceptibility of the individual and the amount of lead which is absorbed. The case already quoted, described by Hamilton, in which symptoms developed after three days' exposure, is very unusual. More often months elapse and frequently years, before the disease frankly manifests itself by one of the major symptoms. However, during this period patients usually suffer from milder symptoms of the disease. There is apt to be a tendency to indigestion, characterized by a sweetish, metallic taste in the mouth, loss of appetite, perhaps slight nausea, and abdominal uneasiness and constipation. There may be a growing sense of lethargy and weakness and frequently some loss of weight. Not infrequently the patients complain of headache and vague pains in the back and limbs, most particularly in the region about the joints.

COURSE.—*Colic.*—The commonest episode after such a history is the occurrence of an attack of lead colic. Occasionally colic occurs without any of the preceding symptoms, but this is an unusual course. Lead colic is characterized by very violent abdominal pain, usually rather diffuse in distribution, but most marked in the middle of the abdomen. Sometimes it is centered below the umbilicus, more rarely above it, and at times it is more severe on one side than on the other. The pain is a steady, violent ache, which usually lasts for a few hours, with moderate variation in intensity, and then gradually subsides to complete or partial comfort before it recurs. The pain may persist undiminished for several days. The whole attack lasts from a few hours to two or three days. The patient often finds some relief in pressure on the abdomen, in spite of a superficial hyperesthesia. There may be vomiting, and there is always constipation. There may be a slight elevation of temperature, but the pulse is slow and hard, the blood-pressure being typically elevated. The skin is pale and dry, the abdomen rigid and retracted, sometimes showing some tenderness about the umbilical region. These attacks show a decided tendency to recur unless the patient is removed from the exposure to lead. Sollmann explains these attacks as being caused by irritation of the endings of the vagus fibers in the intestinal walls, resulting in a constant muscular spasm which lacks the normal peristaltic movement. In support of this theory he cites the relief afforded by atropin, the characteristic action of which causes paralysis of the terminal vagus fibers.

Other Digestive Symptoms.—Other digestive symptoms almost invariably persist. Harris found a complaint of some indigestion in one-third of all the cases of painters examined. Constipation is most striking and constant. There may be recurrent attacks of diarrhea. Bad taste in the mouth, epigastric distress or uneasiness, anorexia and eructations are frequent complaints. There may be slight jaundice. A rather unusual finding is painless swelling of the parotids. Comby found 12 such cases among lead workers. The submaxillary glands may be enlarged.

The Lead Line.—The presence of the so-called blue line, or Burtonian line, on the gums is of absolute diagnostic value. It consists in a bluish discoloration, which, when examined with a hand lens, is found to consist of tiny discrete spots, situated on the gums about half a millimeter from the dental margins. The spots are more frequently found and more numerous opposite the spaces between the teeth. They are common along the bases of the lower incisors and canines, on the labial surface of the gums. If they are not found there or bordering the upper front teeth it is always worth while to look on the inner surface, as they are sometimes found exclusively in this situation. They do not occur on the gums when the teeth are gone. The blue lead line should be carefully distinguished from the purplish border frequently observed about dirty and infected teeth. The latter begins at the very margin and is smooth and not stippled. The lead line is due to the deposit of lead sulphid formed by a combination of lead with putrefactive products such as hydrogen bisulphid. With proper care of the teeth the lead line is not formed.

Lead Palsies.—With or without the symptoms mentioned above, there may develop peripheral neuritis with palsy. The most common and characteristic paralysis is a bilateral wrist-drop. This manifests itself as a gradually developing weakness in the extensors of the fingers and wrists, there being, as a rule, no pain or other sensory disturbances. The supinator longus is usually spared. The muscles of the upper arm and shoulder-girdle may be involved alone, or the degeneration may be associated with wrist-drop. Above the forearm the deltoid is most commonly involved, but the biceps, triceps, brachialis anticus, supra- and infraspinatus may be affected. One type of palsy affects the small muscles of the hand, resulting in weakness and atrophy of the thenar and hyperthenar eminence and the interossei. The legs are not uncommonly affected in children, less often in adults. The perinei and extensors of the toes are most often involved, giving rise to foot-drop. The small muscles of the foot, or the thigh muscles, are more rarely affected. Any motor nerve, including the cranial motor nerves, may show involvement. A rare type of lead palsy is a generalized peripheral neuritis. Some degree of atrophy usually develops, and the muscles show at least a partial reaction of degeneration.

Encephalopathies.—Cerebral symptoms may be sudden and violent or may develop gradually, with or without previous evidence of lead-poisoning. Negroes and women are more apt to exhibit this form of the disease. The latter are apt to show hysterical manifestations. Some degree of depression is not uncommon among lead workers, and a moderately fine tremor is frequently seen. Sudden development of delirium, sometimes amounting to mania, tonic and clonic convulsions and coma, either following delirium or developing independently, are the commonest cerebral manifestations of lead. All of these symptoms may be directly due to lead-poisoning or may occur as a consequence of nephritis, which is so common among lead workers. Arteriosclerosis and apoplexy, also common results of lead-poisoning, may simulate or complicate the picture. In lead encephalopathies the complexion is typically pale and sallow, the blood-pressure is high, the spinal fluid is under increased pressure, and other evidences of lead-poisoning will be found. Encephalopathy is a very serious condition, usually terminating fatally, but remarkable recoveries are sometimes observed.

Chronic toxic psychoses are sometimes seen. They may be characterized by depression and ideas of persecution or by exalted states. Sometimes a condition closely simulating paretic dementia occurs, the mental powers gradually fading. These insanities may be permanent, but even very severe cases are sometimes followed by recovery.

Other Nervous Symptoms.—Headache is very common among lead workers. They also frequently complain of backache, pains in the chest and in the limbs, particularly about the joints. Numbness and paresthesia are sometimes troublesome. A moderately fine tremor is not uncommon. The reflexes are usually somewhat diminished or, in the case of well-marked neuritis, abolished. The pupils may be irregular and unequal.

Cardiovascular Involvement.—Hypertension and arteriosclerosis are commonly found among lead workers. Hypertension may be due to the toxic influence of the metal upon the vasomotor mechanism, or to involvement of the small renal vessels. During an attack of colic the blood-pressure is increased. This is due to the pressure on the vessels caused by a spasm of the intestinal walls and by increased abdominal pressure from the fixation of the abdominal wall and diaphragm. The vascular degeneration is no doubt due in part to the chronic hypertension and in part to the effect of the lead upon the vessel-walls. In Harris's series 39 per cent. of the cases exhibited a systolic blood-pressure of 140 mm. Lower blood-pressures were found in the younger men. With the hypertension comes cardiac hypertrophy, the heart being displaced downward and to the left, the area of cardiac dullness increased, and the aortic second sound being loud and ringing. There are usually no murmurs, except perhaps the harsh systolic bruit at the base, denoting roughening of the aortic arch. The radials and other superficial arteries gradually become hard, tortuous and nodular.

Accidents common to hypertension, cardiac failure and apoplexy, not infrequently overtake the subjects of lead-poisoning. In fact they represent two of the commonest terminations of the disease. The heart usually fails gradually, giving rise to increasing dyspnea and dropsy, which may involve the serous cavities. If the coronaries are more affected the cardiac symptoms will be those of angina pectoris, and are apt to terminate in sudden death.

Vascular accidents such as thrombosis or cerebral apoplexy, with their well-known train of symptoms, quite frequently occur in the later stages of the disease.

Renal Involvement.—Albuminuria and cylindruria are commonly associated with lead colic. They are found at times, with or without other symptoms of nephritis, in a fair proportion of cases of chronic lead-poisoning. Lead acts as a direct irritant to the tubular epithelium and even more so to the vessels of the kidney. The vascular form of nephropathy with hypertension, cardiac hypertrophy and some degree of nitrogen retention is undoubtedly frequently caused by lead. The severer form of chronic diffuse glomerulonephritis, with polyuria, hyposthenuria, and marked degrees of nitrogen retention and uremia, frequently occurs in lead subjects. The vascular changes induced by the lead undoubtedly predispose to this process, but infection probably plays some part in its causation. Oephuls, in 1912, produced tubular degeneration in guinea pigs by means of lead, but was unable to produce the glomerular changes frequently observed in man.

Respiratory Involvement.—Chronic bronchitis is common among trades in which the workers are subject to lead dust or fumes. This is not infrequently associated with emphysema. Bronchial asthma is a rather frequent complaint. The relation of lead to its development is not known. Pulmonary tuberculosis is a very frequent complication.

Reproductive System.—The tendency to abortion and miscarriage among women who are subject to lead-poisoning has been remarked. (See Etiology—Heredity.) The male may suffer from sterility without impotence. If he remains potent, the resulting product of conception is apt to be lost by the healthy mother through abortion.

Blood.—One of the most constant and striking features of chronic lead-poisoning is anemia. This is apt to appear early and is responsible for many of the slight, vague symptoms which frequently trouble lead workers who otherwise scarcely realize that they are sick. The severity of the anemia is usually directly proportionate to the degree of poisoning. It may reach an extreme form, but is more often slight or moderate. It manifests itself in pallor, weakness, a tendency to breathlessness, and, in the more serious forms, by tinnitus aureum, palpitation and a tendency to edema. On examination the blood is found to present the characteristics of a secondary anemia, with certain rather characteristic modifications. The hemoglobin is below 70 per cent. in the majority of instances, and is always proportionately lower than the number of red-cells. The red-cells commonly number between four and five million, but are not infrequently below four million and sometimes below three million. A slight leukocytosis of from ten to fifteen thousand is usually found, and higher figures are not unknown. The differential count is normal.

Pepper and White have shown that on staining a blood-film with a basic blood-stain it is frequently found that many of the red-cells contain the fine discrete granules first described by Grawitz. This basophilia has been emphasized by some authorities as a diagnostic *sine qua non,* and while it is probable that it could be demonstrated in all cases if the search were persistent enough, its absence should not cause one to reject lead-poisoning in making a diagnosis. Basophilia occurs in all forms of grave anemia. Basophilia without anemia, or with only slight anemia, is extremely suggestive of lead-poisoning, and its presence is always of corroborative value in diagnosis. The presence of nucleated red-cells is not uncommon in lead-poisoning, even when there is only slight anemia. Both of these factors point to active blood regeneration.

Eyes.—The muscles of the eye may be affected through peripheral palsy of the third, fourth or sixth cranial nerves, giving rise to *diplopia.* Toxic *amblyopia* may occur, with temporary blindness, there being no visible change in the eye-grounds. Lead sometimes induces a *retrobulbar neuritis,* usually unilateral, in which the center of the visual field is first affected, with rapid extension to the periphery. Sight may be partially or completely lost. There may be some tenderness on pressure of the eyeballs. At first the eye-grounds appear to be normal, but ultimately the disk becomes pale and blurred. This condition tends to improve with treatment, but scotomata may persist. Retinal hemorrhages are not uncommon.

Loss of Weight.—There is almost always loss of weight in lead-poisoning. The knowledge of this fact would have relieved the mind of the new hand in the storage battery factory who thought he was leaded because he had "put on eight pounds in two weeks." Harris found a loss of from seven to twenty pounds in 70 cases of his series.

Lead Cachexia.—The combination of malnutrition, anemia, digestive disturbances and gradually developing arteriosclerosis, with or without any of the major symptoms of lead-poisoning, forms a picture which is not infrequently met with, and which is spoken of as lead cachexia.

Lead in the Urine.—Opinions vary as to the diagnostic value of an examination of the urine for the presence of lead. It has repeatedly failed at the Long Island College Hospital, particularly in the case of chronic degenerative changes. Lead is more often found in the acuter manifestations, and its presence may prove very helpful in diagnosis.

Diagnosis.—A history of exposure to lead is one of the most important factors in the diagnosis, and considerable investigation concerning the details of the patient's occupation and habits is sometimes required to elicit this information. On the other hand, one should not be too ready to ascribe all complaints to lead-poisoning merely because a patient is a worker in lead. Given a picture of indigestion, slight secondary anemia, and vague pains, with a history of exposure to lead, one should look for corroborative signs such as lead line, lead in the urine, and stippling. Even in the absence of these signs, one may consider the case one of lead-poisoning, if tuberculosis, intestinal parasites and carcinoma can be ruled out.

DIFFERENTIAL DIAGNOSIS.—Lead colic is very apt to simulate one of the *acute abdominal accidents.* The diagnosis may usually be made on the basis of the history, the characteristic pallor, the hard, slow pulse, and the more specific signs of the lead, such as the blue line, stippling, or lead in the urine. The local signs are not as clearly defined as is usual in appendicitis or in a ruptured or strangulated viscus.

The palsy in lead-poisoning is usually a bilateral wrist-drop which is rare in any other variety of multiple neuritis such as *alcoholism, beriberi, diphtheria,* etc. Unusual palsies will have to be identified by means of the history, and by a search for some of the more characteristic features.

Acute lead encephalopathy may suggest *meningitis* or the delirium of some acute infection, or more likely *uremia, apoplexy* or *cerebral trauma.* Spinal puncture shows only an increased pressure, local evidences of infection are lacking, the blood-pressure is high, the complexion sallow. Uremia may be ruled out by the absence of nitrogen retention as shown by blood analysis, by the character of the urine, which is not typically scanty or of low specific gravity, by the absence of the albuminuric retinitis which is so common in uremia, and by the positive findings of a lead line, stippling or lead in the urine. Apoplexy usually gives evidence of local cerebral injury.

Chronic lead psychoses are distinguished by the history and other signs of lead-poisoning. One type resembles *paretic dementia,* and the Wassermann is said to be positive, at times, in lead-poisoning in the absence of *syphilis.* The absence of pleocytosis and globulin in the spinal fluid and the characteristic colloidal gold curve should be helpful in ruling out paresis, while the diagnosis may be clinched by the presence of some of the more usual characteristics of lead.

Association with other Diseases.—The effect of lead as a causative agent in the development of *arteriosclerotic kidney,* and its association with *glomerulonephritis,* have been spoken of. Chronic *bronchitis, emphysema* and *asthma* are not infrequently associated with lead-poisoning. Lead workers who are exposed to lead dust are peculiarly susceptible to *tuberculosis.* Tuberculosis does not seem to be disproportionately frequent among painters.

Gout is so frequently observed among lead workers in countries in which gout is prevalent that lead is sometimes considered to be cause of gout. The fact that lead does not seem to produce gout in this country would argue against such a theory and relegate the poison to the class of predisposing factors. Some degree of retention of uric acid is common in lead-poisoning, but it is also common in other conditions which are not characterized by attacks of gout.

Treatment.—PROPHYLAXIS.—The prophylaxis of lead-poisoning is an extremely serious industrial problem, and has received much attention. In spite of this, much remains to be done, as is demonstrated by the large number of workers who are continually being affected with the disease.

The problem is being attacked from a legislative standpoint along several lines, which should be extended to protect all industrial workers in lead. The first step, as in all such problems, should aim at fuller **knowledge** and **publicity** by requiring physicians and hospitals to report all cases of lead-poisoning. In the dusty trades laws should require **proper ventilation,** and where necessary individual protection by the **wearing of masks and gloves.** In all lead trades proper facilities should be afforded employees for **washing before meals** and departure from work, and suitable surroundings should be provided for the lunch hour. **Government inspection** should be maintained and adequate penalties provided for infringement of the laws. In some instances liability laws have done much toward stimulating employers to take the proper precautions.

Lead workers are frequently ignorant of the dangers to which they are exposed and of the proper methods of protecting themselves. Furthermore they are very apt to grow careless, even though they are quite familiar with the danger. It is well within the province of governments, through health and labor agencies, to undertake to **educate** and keep reminding lead workers of these things. It would no doubt make a vast difference in the morbidity.

Personal prophylaxis is a matter of **personal cleanliness** and hygiene. If a worker can be protected against the inhalation of dust and fumes, he can overcome the other dangers by the care he takes of his hands and face and of his clothes, and by keeping in good condition.

GENERAL MANAGEMENT.—The most important indication is to **stop**

the ingestion of lead by the patient. In mild cases, in which this can be controlled by the observance of proper protective measures, it may be permissible for the patient to continue at work. In severer cases, or where the exposure to lead cannot be guarded against, the work should be stopped, and it is far wiser for the patient never to resume it. This may not always be possible, but the physician's advice on the subject should be emphatic, and it will be found to be possible more often than is frequently supposed. The patient's activities should be restricted proportionately to the degree of his debility. In the presence of malnutrition and anemia **rest** is clearly indicated, the severer type requiring **confinement to bed.** This condition also calls for a maximum of **fresh air and sunshine.** General advice will be found to be less effective than specific directions about open windows, hours out of doors, etc.

The **diet** may have to be modified to meet the particular type of indigestion which may present itself, but bearing in mind the tendency to malnutrition and the constipation, it should be as **liberal** in caloric value and bulk as the patient can comfortably accommodate. **Green vegetables, milk, butter** and **eggs** are valuable for their vitamin content. Thorough **mastication** should be insisted upon.

The **teeth** should be **put in order** by a competent dentist, as oral sepsis from infected roots and gums is a common complication and is more dangerous than is realized by the patient.

The bowels will certainly require attention, and for some time a daily **laxative** will be necessary. **Magnesium sulphate** has long been used and has given satisfactory results. Although it probably lacks the specific protective action in the stomach, where the sulphate formed is liable to resolution in the gastric juice, no doubt it does render insoluble lead that has found its way into the intestine.

MEDICINAL TREATMENT.—**Potassium iodid** has been the standby in lead-poisoning since 1844, when Melsens showed that the iodids increase the rapidity of elimination of lead. This is accomplished by the formation of soluble lead iodid, which is then eliminated by the kidneys and to a lesser degree by the bowel. Large doses are said to be dangerous, as a larger amount of lead than can be readily eliminated might be thrown into solution. The author has seen much larger doses given than are ordinarily advised, but they are unnecessary and possibly dangerous. Ten grains (0.65 gram), three times a day is the optimum dose for most adults. It is best administered in milk, after meals:

℞	Potassii iodidi	℥ ss.......	15.5	gram.
	Aquæ	℥ ss......	15	c.c.

M. Sig.: Ten drops in milk after each meal.

Signs of iodism, such as coryza or acne, should be signals to discontinue the drug for a week. The drug should be continued if possible until cure is well established.

Magnesium sulphate should be given daily. A tablespoonful in a glass of water on arising will ordinarily be sufficient.

The anemia may demand the administration of **iron.** This may be given as the carbonate or citrate, and the addition of **strychnin** is often helpful, particularly in the presence of a convalescing neuritis:

℞ Ferri carbonatis	ʒ iii (11.65 grams)
Strychninæ sulphatis	grain 1 (0.065 gram)

M. Div. in Cap. No. 30.
Sig.: One capsule after each meal.

Symptomatic Treatment.—*Colic.*—Like every affection characterized by muscle-spasm, lead colic tends to yield to the **application of heat.** Towels wrung out of hot water may be applied to the abdomen and changed frequently, or the patient may be immersed in a hot bath. Prompt, if partial, relief is sometimes found in the inhalation of **amyl nitrite,** a pearl being crushed in a handkerchief, which is held to the face. Or a tablet of **nitroglycerin,** 1/100 grain (0.00065 gram), may be given every half hour or every hour, to be held under the tongue until dissolved. If the feeling of congestion in the head sometimes caused by this drug does not occur, and it gives temporary relief, the dose may be repeated every fifteen minutes. As already explained, atropin has a specific effect in relaxing intestinal spasm, through its action on the vagus endings. A hypodermic of from 1/100 to 1/50 of a grain should be given, and the former dose may be repeated every three hours until relief is obtained or the physiological action of the drug appears. Flushed face, dry throat, dilated pupils or delirium indicate the withdrawal of the drug.

Lead Palsy.—Lead palsy should not be treated locally while it is progressing. During this period the general treatment already outlined should be vigorously carried out. After from two to four weeks of this treatment it will be evident that the active neuritis has passed and that the palsy is stationary or retrogressive. At this time local measures should be instituted. Daily gentle **massage** and **passive movements of the joints** should be begun. The time should not exceed fifteen minutes the first day, but may be rapidly extended to from twenty to thirty minutes, when the application of the sinusoidal current should be added. In the case of wrist-drop, the forearms may be placed in **bath electrodes,** or **wet sponge electrodes** may be used, one being placed just above the elbow, the other moved about over the paralyzed muscle. From 5 to 10 volts should be used, and the application frequently interrupted to rest the muscles. From five to ten minutes for each arm is sufficient. With the reappearance of function, the patient should be given active **exercises** and encouraged to use the arm.

During convalescence, **strychnin** is useful. It should be pushed to the point of toleration. An effective way to accomplish this is to prescribe a solution of such strength that 10 drops will contain 1/40 of a grain (0.0016 gram) and to direct that the patient start with 10 drops three times a day after meals and increase the dose by 1 drop each day until symptoms arise, when the dose is diminished to 10 drops and again increased if the symptoms disappear. Muscular twitching or headache are the indications for reducing the dose.

℞ Strychninæ sulphatis.........grain 1¼ (0.081 gram)
Aquæ ....℥ i (30 c.c.)

M. Sig.: Ten drops in water three times a day. Increase the dose by 1 drop each day.

Encephalopathy.—A patient in violent delirium or convulsions demands immediate sedative treatment. Any of the **bromid salts** may be given in doses of from 20 to 30 grains (1.3 to 1.95 grams) combined with from 10 to 15 grains of chloral (0.65 to 0.972 gram). It may be necessary to administer these drugs per rectum, in which case the dose should be doubled and should be given in 1 ounce (30 c.c.) of **starch water.** If necessary, the chloral may be repeated once after two hours and the bromid every two or three hours for a day or two. It may be necessary to resort to **morphin sulphate** hypodermatically in doses of from 1/6 to ¼ grain (0.01 to 0.016 gram), but this should be avoided if possible. Wrapping the patient in **blankets wrung out of hot water** and applying **cold compresses to the head** may be very effective.

In delirium, convulsions or coma, if the hemoglobin is above 70 per cent., the pulse hard and full, **phlebotomy** with the removal of from 300 to 500 c.c. of blood is indicated. **Lumbar puncture** to reduce the excessive intracranial pressure has been advocated. The same result might be obtained much more effectively by the slow intravenous injection of a hypertonic solution, such as 25 per cent. **glucose,** 500 c.c. being given in two hours. This has been established experimentally at the Army Laboratory of Experimental Neurology, and the author has found it very successful at the Base Hospital at Camp Lee in cerebrospinal meningitis, and mumps encephalitis. Its diuretic action would also be valuable. **Elimination** should be **encouraged** as much as possible. **Magnesium sulphate** should be given in concentrated solution, a teaspoonful every fifteen minutes until free evacuation of the bowels has been secured. **Water** should be given in large quantities, by mouth if possible, if not by rectal seepage; or **normal saline** may be given by hypodermoclysis or intravenous injection.

During acute encephalopathy, **potassium iodid** should **not** be given.

Lead psychoses should be treated on the principles already described for chronic lead-poisoning. Domestic circumstances will determine whether or not it will be necessary to send the patient to an institution.

Prognosis.—A patient with *lead colic* may appear seriously ill, but he very rarely dies. The acute attack usually passes off within a few hours or a few days, but unless the exposure to lead is prevented it is very apt to recur.

Lead palsy is usually curable, and with proper treatment should clear up in from three to six months.

Acute lead encephalopathy is a very dangerous condition and is frequently fatal, particularly if the patient becomes comatose. With recovery from the acute attack the outlook is favorable if the patient can be guarded from further exposure to lead, and if organic changes such as cerebral arteriosclerosis have not taken place.

The lead psychoses are ordinarily curable, although they may terminate in chronic insanity. The prognosis is more serious if the patient belongs to a neuropathic family or if there is other evidence of nervous instability, where one might suspect that the lead had merely precipitated the development of some other form of mental disease. In older patients, with well-marked arteriosclerosis, the degenerative changes of senility may complicate the situation and darken the outlook. However, recovery is common, and may ensue after apparently advanced dementia.

In all lead workers the liability to tuberculosis, arteriosclerosis and nephritis tends to shorten life. With the development of any of these conditions the prognosis is more serious if the patient continues at his work, so that the course of these diseases is unusually short. Tuberculosis is the commonest cause of death among lead workers, but apoplexy, heart-failure and uremia claim many victims, especially among the older workers.

Pathology.—There is little that is distinctive in the pathology of lead-poisoning. The body is usually somewhat wasted, there being but little adipose tissue, and the muscles being flabby and light-colored. On *gross examination* one may find atrophy of the muscles supplied by the nerves which are peculiarly liable to peripheral neuritis. Thus the extensors of the wrists and fingers, or other groups of muscles, may be atrophied. The lead line may be visible on the gums and the intestinal mucosa may be stained with lead sulphid. The brain may show edema with flattening of the convolutions, and a tendency to thickening of the pia.

The *microscopical examination* may reveal many pathological changes, but little or nothing that is characteristic.

CIRCULATORY SYSTEM.—The circulatory system is apt to show the degenerative changes of arteriosclerosis. The heart is usually hypertrophied and may show some fibrosis. Occasionally minute hemorrhages are found in the brain, peripheral nerves and muscles.

RESPIRATORY SYSTEM.—The respiratory system may exhibit the changes of chronic bronchitis and emphysema, while tuberculosis is a common complication.

DIGESTIVE SYSTEM.—Carious teeth and infected gums are common. Atrophic gastritis is frequently met with. The gums and intestinal mucosa may be stained with lead sulphid as already described.

KIDNEYS.—The kidneys show fatty degeneration in very acute cases. The typical change in chronic lead-poisoning is that of arteriosclerosis with atrophy of the affected segments and hyalinization of the corresponding glomeruli. There is usually more or less fibrosis. There may be superadded evidence of an infectious process as seen in the proliferation of the tufts with a tendency to adhere to the capsule, thrombosis of the glomeruli, and interstitial collections of round-cells or of leukocytes.

NEUROMUSCULAR SYSTEM.—The pia may be a little thickened, edematous and congested. The brain is apt to show vascular changes, and there may be gross evidence of hemorrhage or thrombosis. Minute capillary hemorrhages have been found at times. Some cases have shown a tendency to proliferation of the neuroglia, and nuclear changes in the cortical cells have been described. In the ganglion-cells of the cord chromatolysis has been observed, and the peripheral nerves sometimes show minute hemorrhages, atrophy of the nerve-fibers, and proliferation of connective tissue.

The muscles may show atrophic changes and fibrosis.

Oliver has recovered lead from the muscles, brain, kidneys and liver. In cases in which the patient dies of some degenerative disease brought about by lead, perhaps years before, little or no lead can be recovered.

Historical Summary and Distribution.—The symptoms of lead-poisoning were recognized by the early Greek and Roman physicians and were described by Galen, Celcus, Æginita and Actuarius. Probably the disease dates back to long before these writers, as lead carbonate was used in painting centuries before Christ.

In the first half of the 7th century an epidemic was prevalent in many parts of the Roman Empire. About a thousand years later the disease became quite widespread in various parts of the world. In 1572 an epidemic appeared in the South of France, but its nature was not recognized until nearly a hundred years later. This was known as "Poitou colic," and was due to the drinking of wine and cider which had been contaminated with lead in the vats and presses, and to the use of water-pipes lined with lead. During the 18th and 19th centuries, Spain and Holland suffered similar epidemics. The well-known "Devonshire colic" in England was first described by Huxham in 1739, but its cause was not discovered until Baker recovered lead from the cider in 1767 and showed that the cider presses and vats were responsible.

The "dry gripes" of the West Indies was described as early as 1717 by Smith. Cadwalader of Philadelphia, in 1745, published a work which was printed by Benjamin Franklin, in which he described the palsies and colic of the West Indies and ascribed them to the drinking of Jamaica rum which was distilled through lead pipes.

A letter from Benjamin Franklin to his friend Vaughan (July 31, 1786) recalls having heard as a boy that the North Carolinians complained that the rum imported from Massachusetts caused "dry belly-ache" and that the latter colony was forced to adopt legislative restrictions as to the use of lead in the still-heads and worms used in the manufacture of rum.

In the first half of the last century, lead-poisoning became quite common among mariners, particularly in the tropics. This was long thought to be due to some infection. In the French Navy it was particularly prevalent and was the subject of much discussion.

Industrial lead-poisoning has long been prevalent in all civilized countries. Such trades as painting, plumbing and typesetting are universally distributed, and smelting and refining lead, and such manufacturing processes as necessitate the use of lead, while confined to certain localities, are found in most countries. There is a vast difference, however, in the efficiency with which protective regulations are enacted and enforced. Oliver in England and Alice Hamilton in this country have done most to investigate the dangers of industrial lead-poisoning and to stimulate the adoption of proper precautions.

BIBLIOGRAPHY

COMBY. Bull. et mém. Soc. méd. d. hôp. de Paris, 1917, xli, 1122.
EDSALL. Modern medicine. Philadelphia, 1914, ii, 355.
ELSMER. Monographic medicine. New York, 1917, ii, 1187.
GARRISON. An introduction to the history of medicine. Philadelphia, 1917.
HAMILTON. U. S. Bull., Bureau of Labor, 1911, No. 95.
——— U. S. Bull., Bureau of Labor, 1912, No. 104.
——— Jour. Amer. Med. Assn., 1912, lix, No. 10, p. 777.
HARRIS. Arch. Int. Med., August, 1918, xxii, No. 2, p. 129.
HIRSCH. Handbook of geographical and historical pathology (English Translation). London, 1885, ii, Chap. VIII, p. 264.
OEPHULS. Proc. Soc. Exper. Biol. and Med., 1912, x, 51.
OLIVER. Dangerous trades. London, 1902.
——— U. S. Bull., Bureau of Labor, 1911, No. 95.
THOMPSON. The occupational diseases. New York, 1914, Part iii, p. 196.

CHAPTER IV

MERCURY-POISONING

By Tasker Howard, M.D.

Etiology, p. 75—Acute mercurial poisoning, p. 76:—Acute bichlorid poisoning p. 76:—Symptomatology, p. 76; Diagnosis, p. 77; Treatment, p. 78:—Prophylaxis, p. 78; Immediate treatment, p. 78; Routine treatment, p. 78—Prognosis, p. 79; Pathology, p. 79.
Chronic mercurial poisoning, p. 79:—Symptomatology, p. 79; Diagnosis, p. 80; Treatment, p. 80:—Prophylaxis, p. 80—Prognosis, p. 81—Pathology, p. 81.

Etiology.—The sources of mercury-poisoning are roughly two, corresponding to the acute and chronic form of poisoning. *Acute poisoning* is nearly always the result of an overdose of some mercurial drug taken either through accident or by design, while *chronic mercury-poisoning* is usually acquired only in some trade involving the handling of this metal or its salts.

Mild degrees of mercurialism are frequently induced by physicians in the *treatment of syphilis.* The drug is pushed until "the gums are touched" in order to obtain the full therapeutic effect. Accidental salivation from *overdoses of calomel* are much less frequent than in the days when more heroic doses of this drug were habitually used. Serious cases of acute mercurial poisoning have become very frequent of late due to the use of bichlorid of mercury tablets as a suicidal agent. Many instances have also occurred in consequence of patients carelessly mistaking these tablets for other remedies. The ill-advised use of a *bichlorid douche* for the purpose of preventing conception is responsible for the presence of these tablets in many homes. The author has observed a fatal case of poisoning following a copious douche of 1 to 1,000 bichlorid solution, and one patient induced a severe vaginitis by introducing a tablet into the vagina. Lambert and Patterson report fatal poisoning from the same source. Sansum has shown that in the dog 4 mg. (1/16 grain) of mercury per kilo of body weight is invariably fatal, when injected into the circulation. He believes that about the same ratio holds for man, and that when larger doses are taken by mouth and recovery ensues, the drug has not been absorbed. Five mg. per kilo were required to regularly produce anuria.

Industrial mercury-poisoning is not as prevalent as lead-poisoning, because the trades which involve the use of the metal are not as numerous as the lead industries. Mercury is so volatile, however, and so poisonous, that it is more dangerous to workers, unless they are very carefully guarded, than is lead. Workers in quicksilver mines are frequently victims of poisoning. Mercury is also used in certain processes in the extraction of other metals from their ores. Makers of felt hats, and of mirrors, barometers and other scientific instruments requiring mercury columns, are subject to the dangers of poisoning. One of the first American physicians to experiment with the sphygmomanometer developed symptoms of poisoning from the effects of quicksilver spilled about his room. Makers of mercurial drugs, amalgams for dental use, and certain cosmetics, are exposed to the effects of mercury.

ACUTE MERCURIAL POISONING

The first symptom in mild cases induced by an overdose of calomel or by the radical employment of some mercurial antisyphilitic, is tenderness of the gums and alveolar processes, so that it is a little painful to bite hard. The gums may become a bit swollen and "spongy" and tend to bleed easily. With this degree of involvement there is usually salivation. The process may progress, in severe cases, to loosening and falling out of the teeth and severe ulcerative stomatitis. In this stage the breath is foul, salivation marked and the patient's mouth so sore that he may not be able to swallow. With this degree of poisoning the systemic effects, such as albuminuria, some degree of enteritis, anemia, and prostration, will also be in evidence.

Acute Bichlorid Poisoning.—This combines the effects of a violent corrosive action of the gastro-intestinal tract with the systemic effect of the poison.

SYMPTOMATOLOGY.—*Gastro-intestinal Tract.*—Vomiting is usually the first symptom, appearing within an hour after the ingestion of the drug. It sometimes occurs within a few minutes. In severe cases the vomiting may be persistent, but it tends to subside under proper treatment. A burning pain is usually felt in the throat and epigastrium, and there is gingivitis and salivation. The condition of the mouth may be like that described above. Diarrhea, not infrequently bloody, is a constant symptom.

Circulatory System.—The immediate effect of the violent corrosive action of bichlorid upon the stomach and intestine is the production of some degree of shock, with splanchnic vasomotor dilatation, the accumulation of blood in this area, and its reduction elsewhere. This results in pallor, a weak, rapid pulse and low blood-pressure, subnormal temperature, and a tendency to syncope, and in some cases death in collapse. The shock ordinarily passes off quickly. Later in the disease the circulatory system may show the effect of exhaustion due to the continued gastro-enteritis. The poison also acts directly upon the heart and vessels. Rosenbloom recovered 5.81 mg. (1/12 grain) of mercury from the heart in a fatal case of poisoning. With the involvement of the kidneys and the development of uremia there is a tendency toward an elevation of the blood-pressure. In a recent series of 11 fatal cases under the author's observation, at Long Island College Hospital, the 2 fatal cases showed practically normal blood-pressure. The heart and vessels had not the strength to respond with a high tension. In the case of one patient who recovered, the blood-pressure reached 160 mm.

Kidneys.—The effect of bichlorid upon the kidneys is very striking. There is practically always albuminuria, which may be very marked, and this is not infrequently associated with hematuria. There may be a persistent dull pain or feeling of weight in the small of the back. The dangerous sign, as far as the kidneys are concerned, is a diminution in the amount of urine excreted. This varies from moderate degrees of oliguria to total anuria, and the prognosis varies directly with the severity of this symptom. Oliguria, showing the presence of kidney injury, may occur early, or may come on at any time from the fourth to the tenth day after the gastro-intestinal symptoms have begun to subside. With the decrease in the amount of urine there is a diminution in the excretion of all the elements of the urine, so that although there may be complete anuria for a number of days without any symptoms whatever, a study of the blood during this period shows a rapidly increasing accumulation of dangerous nitrogenous products. The uric acid is quickly increased. The urea mounts to 100, 200, or 300 milligrams and over, per 100 c.c. of blood. Lastly, the creatinin rises from its normal, of under 1, to 15 or more milligrams. The author has also found the blood-sugar and cholesterol increased. The phenolphthalein is of course zero with total anuria, and with partial suppression it gives low readings. The outcome with continued suppression is uremia, characterized by nausea, twitching of the muscles, hiccup, drowsiness, coma and death. Convulsions seldom occur and edema is not seen, in spite of the failure of the kidneys to excrete water.

Acidosis.—During the course of the disease a metabolic disturbance is apt to develop which lacks the chemical characteristics of uremia and which may go on to a fatal termination. This has been shown to be an acidosis dependent upon some disturbance in ketone metabolism. The origin of the acidosis is not known. It is not dependent upon kidney involvement, as MacNider has shown experimentally that it precedes the latter. Furthermore, the acidosis of nephritis is not a ketosis. Clinically the acidosis manifests itself most typically in coma. This may be preceded by constant or intermittent periods of dyspnea. The urine shows the presence of acetone and diacetic acid, with rising ammonia nitrogen. The serum shows a low carbon-dioxid-combining capacity, and the alveolar air a low carbon-dioxid reading.

Mercury in the Excretions.—Mercury may be recovered from the vomitus, the stools, and the sweat (Lambert and Patterson). It has been shown by Lieb and Goodwin that mercury is excreted by the stomach as well as by the intestines. This is important from a therapeutic standpoint. Recovery of the metal in the urine and stools is sometimes helpful in determining a diagnosis.

DIAGNOSIS.—Acute mercurial poisoning is usually diagnosed promptly by the history. In case of doubt, the vomitus or stomach washings should be analyzed to determine the presence or absence of mercury.

TREATMENT.—*Prophylaxis.*—The frequency with which bichlorid has been used with suicidal intent has led some municipalities to restrict the sale of this drug to the laity, there being numerous less toxic antiseptics which are quite as efficient for domestic use. Less stringent regulations require the dispensing of the tablets in bottles of such shape that they cannot readily be mistaken, even in the dark. The addition of a trace of some dye to the tablet results in a colored solution, which cannot be mistaken for water.

Immediate Treatment.—Three or four **eggs** and a pint of **milk** should be administered immediately, in order to form the insoluble albuminate of mercury. This should be followed by thorough **lavage,** leaving a pint of milk in the stomach. The shock may require the application of **hot blankets,** and stimulation with **adrenalin chlorid,** grain 1/64 (0.001 gram), or **strychnin,** grain 1/20 (0.003 gram).

Routine Treatment.—Sansum's experiments on dogs, in which various therapeutic measures were instituted after the intravenous administration of the uniformly fatal minimum dose, appear rather discouraging, and yet very much may be done toward saving life. Man does not acquire bichlorid-poisoning in this manner. Furthermore, the acceleration of excretion, plus the prevention of reabsorption which normally takes place in the stomach and bowel, may well prevent a sublethal dose, in the sense of Sansum, from becoming lethal. The principles of treatment outlined by Lambert and Patterson have proved very satisfactory, not only in their own practice but in the experience of many others who have adopted their suggestions. These include **routine lavage** and **colonic irrigations** to wash out mercury excreted in the alimentary tract, and the administration of **alkaline diuretics** and **hot packs** to encourage elimination. Continuous rectal seepage with a solution of **potassium acetate** is also emphasized. The alkalis have the added advantage of combating acidosis. The following directions somewhat modify the routine outlined by Lambert and Patterson.

Gastric lavage should be given every eight hours, as should colonic irrigation. Potassium acetate solution of a strength of 1 dram to the pint (3.90 grams to 500 c.c.), should be given per rectum by the drip method, continuously, or in milder cases a pint every eight hours. Lambert and Patterson's alkaline diuretic consists of potassium bitartrate, 1 dram (3.90 grams), sugar, 1 dram (3.90 grams), lactose ½ ounce (15.5 grams), lemon juice 1 fluidounce (30 c.c.) to a pint of water (500 c.c.). This is administered every eight hours, alternating with a pint of milk. A hot pack should be applied once a day. **Carter's antidote,** consisting of sodium phosphite, will change bichlorid to calomel *in vitro.* The reaction may affect the mercury in the gastro-intestinal tract and be helpful in this manner, although its intravenous use immediately after a lethal dose of mercury failed to save dogs in Sansum's experiments. Carter recommends 5 to 10 grains (0.324-0.65 gram) of sodium phosphite for every grain of mercury taken, plus 5 grains (0.324 gram) of sodium acetate, in half a glass of water every hour.

Phlebotomy and the intravenous injection of glucose or saline solutions have been recommended, and while theoretically these procedures seem sound, they have failed experimentally and availed nothing in one case at Long Island Hospital. It may be that in a borderline case they might throw the balance in the right direction. Decapsulation of the kidneys has nothing to recommend it. It is theoretically unsound and practically useless. The routine outlined above should be continued for at least a week and in severe cases for from two to three weeks.

PROGNOSIS.—In acute mercurial poisoning, much depends upon the promptness with which the stomach is evacuated. If this is done thoroughly within an hour recovery usually ensues, even though quite massive doses have been taken. A solution of bichlorid is more dangerous than tablets because it is absorbed more promptly, although its corrosive action is less marked. Fatal collapse may occur early. If this period is safely passed the most serious symptom is suppression of urine. This usually appears about the third or fourth day but may be delayed until the eighth or tenth day. Complete anuria is usually fatal, the prognosis depending thereafter upon the success with which efforts to reëstablish a flow of urine is attended. Severe acidosis may prove fatal without suppression of urine.

PATHOLOGY.—Acute mercurialism shows, at autopsy, acute gastroenteritis, gingivitis and stomatitis, and extensive fatty changes in the parenchyma of the organs. The kidneys show swelling and necrosis of the tubular epithelium, the glomeruli appearing intact. The liver displays fatty and parenchymatous changes in the epithelium. The metal has sometimes been recovered in considerable amounts from the brain, stomach, intestines, liver, spleen, kidneys, heart, muscle and blood (Rosenbloom).

CHRONIC MERCURIAL POISONING

Symptomatology.—Chronic mercurial poisoning results in a picture not unlike that produced by other metallic poisons. Progressive asthenia, with loss of weight, pallor induced by anemia of the secondary type, headache, depression, indigestion and perhaps muscular pains, constitute the early symptoms of the disease.

CIRCULATORY SYSTEM.—The circulatory system shares in the general tendency to degeneration. Palpitation and shortness of breath on exertion are complained of with the general asthenia.

RESPIRATORY SYSTEM.—The respiratory system is less affected by the mercury itself than by the dust to which the worker is exposed in so many of the trades involving the use of quicksilver or its salts. In such workers chronic bronchitis and emphysema are frequently seen.

DIGESTIVE SYSTEM.—Soft, spongy gums and infected roots are common in the mouths of these patients. Necrosis of the jaw sometimes occurs in advanced cases. Excessive salivation is common, and the salivary glands are sometimes swollen. Epigastric uneasiness and a feeling of weight or actual pain in the stomach after eating are frequent symptoms. There may be anorexia, nausea and vomiting. Abdominal cramps and diarrhea are not infrequent.

GENITO-URINARY SYSTEM.—Albuminuria is common in chronic mercurial poisoning. The cirrhotic kidney may develop, as in lead- and arsenic-poisoning, the menses are frequently irregular, and sometimes suppressed. Miscarriage is frequent, and the children of women suffering from mercurialism are said to be undersized and delicate.

NERVOUS SYSTEM.—Headaches and mental depression are early and frequent complaints. A coarse intention tremor is common. Peripheral neuritis, affecting the upper extremities first, may occur in the more advanced cases.

SKIN.—The skin may be affected by the local action of fumes or powdered salts of mercury, which give rise to dermatitis.

EXCRETIONS.—Mercury may be found in the urine, feces, saliva, sweat or milk.

Diagnosis.—Chronic mercurial poisoning will suggest itself in the presence of the milder general symptoms of the disease if the patient's occupation is taken into consideration. Suggestive additional points will be found to be the tendency to stomatitis, salivation and an intention tremor. Finally, an analysis of the urine for the presence of metallic poisons will clinch the diagnosis.

Treatment.—PROPHYLAXIS.—The prophylaxis is practically identical with the measures which are taken for the prevention of lead-poisoning. **Legislation** and **education** should aim at lessening the exposure of workers in quicksilver to its effects, by proper ventilation and such **protective devices** as fans, hoods, etc., and by emphasizing the importance of personal protective measures. The worker exposed to dust or fumes should wear a **mask**, covering for the head, and **gloves** if necessary. He should be taught the necessity of care of the mouth and of personal **cleanliness** generally, particularly the importance of thoroughly washing his hands and face before eating. The ordinary rules of hygiene are particularly important to the worker in mercury, as to the worker in any metallic, poisonous substance.

GENERAL TREATMENT.—After symptoms have developed the treatment consists primarily in removing the patient from the influence of the metal, and convincing him of the importance of avoiding it in the future. The mouth and teeth will require particular attention. A mouth wash of potassium chlorate (1 per cent.) is helpful. Salivation may require **belladonna** or **atropin sulphate**; 10 minims (0.6 c.c.) of the tincture belladonna, or 1/120 grain (0.0005 gram) of atropin sulphate may be given three times a day.

The diet should be nourishing and easily digested. For the debility and anemia, **rest** and **fresh air** are most important. Neuritis requires the same treatment as the neuritis of plumbism (*q. v.*). Elimination of the metal is supposed to be hastened by the administration of **potassium** iodid, of which from 5 to 10 grains (0.324 to 0.650 gram) may be given in milk after each meal.

Prognosis.—Chronic mercurialism offers a favorable prognosis if the patient can be persuaded to change his occupation. If he persists in continuing his work until the severer degrees of malnutrition and anemia supervene, recovery is doubtful.

Pathology.—Chronic mercurialism, at autopsy, shows marked malnutrition and anemia, stomatitis and gingivitis with loss of many of the teeth and possibly necrosis of the jaw, chronic catarrhal gastritis, fatty changes in the parenchymatous organs, and peripheral neuritis. The lateral columns of the cord may show atrophy of the myelin, and changes have been described in the ganglion-cells of the cortex.

BIBLIOGRAPHY

Carter. Chicago Med. Rec., 1914, xxxvi, 444.
Lambert and Patterson. Arch. Int. Med., 1916, xvi, 868.
Lieb and Goodwin. Jour. Am. Med. Assn., 1919, lxiv, No. 25, p. 2041.
MacNider. Jour. Exper. Med., 1918, xxvii, 519.
Rosenbloom. Am. Jour. Med. Sc., 1919, clii, No. 3, p. 348.
Sansum. Jour. Am. Med. Assn., 1918, lxx, No. 12, p. 824.
Thompson. The occupational diseases. New York, 1914, Part iii, p. 286.

CHAPTER V

ARSENIC-POISONING

By Tasker Howard, M.D.

General etiology, p. 83—Acute arsenic-poisoning, p. 84:—Symptomatology, p. 84; Diagnosis, p. 84; Treatment, p. 85; Prognosis, p. 85; Pathology, p. 85.
Chronic arsenic-poisoning, p. 86:—Symptomatology, p. 86; Diagnosis, p. 87; Treatment, p. 88; Prognosis, p. 88; Pathology, p. 88.

Arsenic-poisoning is far less common than it formerly was, since the sources of poisoning have become better understood and appropriate measures have been taken to protect against them.

General Etiology.—Occupation.—In these days the industries which involve the handling of arsenical preparations provide the greatest number of cases of chronic arsenic-poisoning, although it is far less common than is lead-poisoning. Thompson found thirty or more trades in which arsenic-poisoning is apt to occur. The mining and smelting of certain ores, particularly silver, zinc and lead, expose the workers to the effects of arsenic. Makers and users of certain dyes and paints, taxidermists and furriers, manufacturers of Paris green and other insecticides, makers of artificial flowers, and glassmakers, are among those who are exposed to arsenic-poisoning.

Volatile Arsenical Compounds.—At one time poisoning from the inhalation of arsenical emanations from *wall-paper dyes* was not uncommon. Green dyes in particular often contained considerable quantities of arsenic, which was acted upon by certain moulds, most commonly the *Penicillium brevicaule,* causing the liberation of some volatile organic compound of the metal. The same thing sometimes happened in the case of rugs, carpets, bed-room hangings, etc. The use of dyes containing arsenic is now largely restricted by law.

Arsenic in Food.—Rare instances of poisoning from arsenical dyes used by bakers have been reported. The writer has found as much as 1 per cent. of arsenic in certain butter dyes. An epidemic of arsenical poisoning occurred in England as the result of the drinking of contaminated beer. In this case the glucose used in the brewing had been prepared with sulphuric acid which contained arsenic. Numerous cases have been reported in Buenos Aires from the use of water from the River Tercero, in which arsenic has been found. The accidental ingestion of rat-poison or vermin exterminators containing arsenic is not an uncommon cause of acute poisoning. Arsenic was a famous and very effective agent in the days of "professional poisoners," and the possibility of its having been administered with homicidal intent is not to be overlooked in any violent, obscure case of gastro-enteritis. Paris green has also had its vogue as a suicidal agent, and is still used occasionally.

OVERDOSES OF ARSENIC USED AS A MEDICINE.—Such overdoses are sometimes responsible for severe symptoms. The premonitory arsenical symptoms, puffiness of the eyes, abdominal cramps, and diarrhea, are often seen, and are in fact used as a check for stopping the drug or diminishing the dose. Arsenic palsy has followed the ingestion of 4 ounces and 1 dram (122.15 c.c.) of Fowler's solution in seventy-five days (Osler). Since the introduction of arsphenamin and allied compounds, arsenical symptoms have not infrequently followed the use of these drugs. Sicard and Rogers pushed the drug in hopeless cases of paresis up to from 15 to 30 cg. (2.315 to 4.63 grains) a day, which caused violent skin reactions with abscess formation and ulcerative stomatitis. The local application of arsenic paste has been known to cause multiple neuritis.

ACUTE ARSENIC-POISONING

Symptomatology.—Acute arsenic-poisoning may occur following inhalation of fumes of arsenic, such as the extremely poisonous arseniureted hydrogen, which may cause immediate death. The acute symptoms of a poisonous dose of arsenic taken by mouth may appear within a few minutes and usually appear within one hour. There is profuse and violent vomiting, usually accompanied by some shock or collapse, with subnormal temperature, rapid pulse and pale skin. The vomiting is shortly followed by a violent diarrhea, which may be bloody. The vomiting and diarrhea persist and tend to dehydrate the patient, giving rise to thirst, dryness of the tongue, mouth and throat and ultimately to the shrunken countenance, cyanosis and cold extremities which characterize the picture of cholera. The urine is scanty, but there may be frequent, painful urination. There may be marked albuminuria and hematuria. The patient complains of vertigo and pains in the abdomen, head and limbs, and there may be violent muscular cramps. In fatal cases coma ensues, sometimes interrupted by tonic or clonic convulsions, or the patient may live for one or two weeks, finally dying of exhaustion. Patients who recover from the acute poisoning are very apt later to develop peripheral neuritis.

A form of delayed arsenic-poisoning somewhat resembling acute yellow atrophy of the liver is sometimes seen days and even weeks after the administration of arsphenamin derivatives (Bailly and MacKay). It is characterized by jaundice and by intense, frequently fatal, toxemia.

Diagnosis.—In acute arsenic-poisoning the diagnosis is made by the history and by the symptoms of a violent gastro-enteritis. In medicolegal cases an analysis of the material vomited and of the urine should be made. Without this a diagnosis cannot be established.

Treatment.—Acute arsenic-poisoning demands immediate lavage with warm water. The antidote, freshly prepared **ferri hydroxum cum magnesii oxido** (U.S.P.) should be administered in doses of from 6 to 8 drams (23.30 to 31.1 grams). This may be prepared by the addition of a suspension of magnesium oxid to a solution of sulphate of iron. This may be rapidly filtered and the precipitate administered without stopping to wash out the magnesium sulphate which is formed. The tincture of the chlorid of iron may be used instead of the sulphate solution, and ordinary milk of magnesia, somewhat diluted, may safely replace the magnesia mixture of the official antidote. In place of magnesia, ammonia water may be added to the sulphate or chlorid solution. The resulting ferric hydroxid must in this case be washed to remove the ammonium sulphate and excess of ammonia, before it is administered. It should be added freely to the water with which the stomach is washed out, some being left in the stomach when the tube is withdrawn. **Milk** and **albumin water** should be administered. The shock should be combated by the external application of **heat**, and by hypodermics of **adrenalin chlorid**, grain 1/64 (0.001 gram), **strychnin sulphate**, grain 1/20 (0.0032 gram) and **morphin sulphate**, grain ¼ (0.016 gram). The gastro-enteritis will require careful feeding, which should be limited to milk, better diluted with lime water or with a bland cereal gruel, or to the gruels alone. Water should be administered in large quantities if the patient can retain it, and the dehydration may demand hypodermoclysis, or **saline solution** given by intravenous injection or transfusion.

Prognosis.—Acute arsenic-poisoning is serious if the dose is sufficient. The inhalation of arseniureted hydrogen may prove immediately fatal. According to Sollmann, doses of from 5 to 50 mg. (1/12 to ¾ grain) of the trioxid are toxic, while from 0.1 to 0.3 gram (1.543 to 4.63 grains) are usually fatal. Much depends upon the promptness with which the poison is washed out of the stomach. The patient may die within a few hours of collapse or live a week or two and die of gastro-enteritis. After recovery from acute poisoning, the symptoms of chronic poisoning may supervene.

Pathology.—Dilatation of the capillaries, particularly of the splanchnic area, is stated by Sollmann to be the primary effect of arsenic. Functionally this gives rise to the vasomotor phenomenon of shock, and in his opinion it is the origin of the pathology in the alimentary mucous membrane. In acute cases the latter shows congestion and superficial ulceration. The viscera, such as the liver, heart and kidney, show marked fatty changes. There may be obstructive jaundice, due to pressure on the bile-ducts.

CHRONIC ARSENIC-POISONING

Symptomatology.—GENERAL SYMPTOMS.—Chronic arsenic-poisoning may cause a curious variety of symptoms, the most characteristic being those which affect the skin and nervous system. Just as in lead-poisoning, anemia, loss of weight and a general feeling of weakness are common accompaniments of the more specific complaints, and may be the only symptoms.

Circulatory System.—The circulatory system is affected primarily through a depression of the vasomotor system with a tendency to passive splanchnic plethora. The pulse is apt to be weak and the patient may complain of palpitation and breathlessness, to which the anemia contributes.

Respiratory System.—The respiratory system may be affected directly in the case of patients who inhale arsenic fumes or dust. In such patients a chronic rhinitis is the rule. This may be ulcerative, the septum being eroded. Chronic bronchitis may be caused in the same manner.

Digestive System.—Gingivitis may occur, and pain in the throat is a very common complaint. The submaxillary and sublingual glands may be swollen. There may be nausea and distaste for food. Abdominal pains are very common, and are apt to take the form of cramps. Recurrent attacks of diarrhea are not infrequent.

Genito-urinary System.—Albuminuria is found during the acuter manifestations, and chronic poisoning is said to predispose to nephritis. Dysuria is a peculiar and not uncommon symptom.

Dysmenorrhea and menstrual irregularities are common. This may be due to a combination of factors. The anemia and general debility, including some degree of circulatory weakness, no doubt play some part.

Arsenic in the urine is not difficult to detect and has considerable diagnostic value. In 1890, when Putnam found arsenic in the urine of 21 out of 45 patients who showed no symptoms of arsenic-poisoning, he emphasized the extent to which people at that time were exposed to dangerous arsenical fumes from wall-paper. A year previously he had reported a series of 26 patients with definite arsenic-poisoning from this cause, the metal being found in the urine of all. Under present conditions arsenic in the urine has a far greater significance. It is very slowly excreted and may be detected for weeks after a single large dose.

Nervous System.—Actual psychoses are rare in arsenic-poisoning, but milder cerebral disturbances are very frequently met with. Insomnia, forgetfulness, and some loss of power of concentration are common complaints. There may be a tendency to headache. In arsenic-poisoning, the "presenting symptom," as Cabot calls the complaint which brings the patient to the physician, is often the pain or palsy of *peripheral neuritis*. The neuritis of arsenic differs from that of lead in that it very often begins with marked sensory symptoms. Numbness and tingling of the feet and hands are common. Some motor changes are usually detectable at this stage, but, while palsy may follow these premonitory symptoms, it is very frequently lacking. The early stages may be accompanied by severe pains in the limbs, and the nerve-trunks may be tender. Later paralysis may appear, and be followed by atrophy and contractures. The parts most frequently affected are the legs; both extensors and flexors are involved, the former being most affected, so that foot-drop and a steppage gait may develop. The thigh muscles are not often affected, although the knee-jerks are characteristically diminished or absent. The muscles of the forearms and hands are sometimes paralyzed, giving rise to wrist-drop, but this seldom occurs in the absence of lower limb palsy. Palsy of the muscles of the larynx may cause aphonia, and the optic nerve is sometimes affected, particularly by toxic doses of atoxyl, less often by arsphenamin. The motor nerves of the eye are sometimes included in the multiple neuritis of arsenic. A form of peripheral neuritis with marked ataxia may simulate tabes dorsalis.

Skin.—Pigmentation of the skin is not uncommon in arsenic-poisoning. The pigmentation may be diffuse or patchy and may involve the mucous membrane of the mouth. Like the pigmentation of Addison's disease, it may be accentuated on the exposed portions of the body and at points of pressure, such as the waist line, bends of the elbows, etc. Keratosis of the hands and feet is a common skin lesion. It is said to have a tendency to degenerate into epithelioma. Erythema, herpes, acne and pustular eruptions, sometimes amounting to furuncles and abscesses, occur at times. The hair has a tendency to come out and the nails to become brittle and ridged. Transverse white bands are seen across the nails after acute arsenic-poisoning.

Eyes.—The eyes are subject to a low grade of conjunctivitis in subjects exposed to arsenic fumes or dust. This may result in lacrymation and photophobia. The external muscles may be paralyzed, causing strabismus and diplopia, and optic neuritis with resulting temporary or permanent blindness may occur. The latter has most often resulted from a therapeutic accident.

Diagnosis.—The chronic poisoning is sometimes difficult to recognize in the absence of neuritis. When the history of exposure to arsenic while at work is readily forthcoming, a picture of debility, anemia and some gastro-intestinal symptoms will be readily explained and may be verified by a chemical examination of the urine. These indefinite symptoms, with perhaps other vague complaints such as have been described, will prove very difficult to explain without some such clue, unless the possibility of arsenic-poisoning is kept in mind and a thorough search made for possible sources of poisoning.

In cases of *multiple neuritis,* the history and associated symptoms should be very helpful. The other forms of multiple neuritis to be considered are those due to lead, alcohol, diphtheria and beriberi. In none of these are the sensory changes as marked as they are in arsenical palsy. Lead usually attacks the upper rather than the lower extremities and involves groups of muscles (*see* Lead-poisoning) rather than the whole distal portion of the limb. Alcohol usually leaves its mark on other portions of the anatomy. Diphtheritic palsy follows an acute infection and beriberi occurs most frequently in the case of orientals or of individuals who have been restricted to the vitamin-poor diet of the far East. The finding of arsenic in the urine should finally distinguish arsenic palsy from the other neuritides.

The *skin lesions* of arsenic may prove difficult to identify. The pigmentation, particularly when associated with diarrhea and digestive disturbances, may closely resemble Addison's disease. In the former, however, there are apt to be some indications of neuritis. The asthenia is not typically as marked. The history, and the presence of arsenic in the urine, should settle the question.

Treatment.—Chronic arsenic-poisoning demands, first of all, **removal of the source of poisoning,** which may involve readjustment of the patient to his environment as to residence, occupation, etc. The digestive disturbances will require some supervision of the **diet,** easily digestible and non-irritating food being indicated. The debility and anemia find their most potent remedies in **rest** and **fresh air.** The neuritis will prove the most important element from a therapeutic standpoint. It differs from the neuritis of lead in the prominence of the sensory symptoms. Rest is indicated until pain and tenderness have disappeared. **Wrapping** the affected part in cotton wool, the use of **methyl salicylate** locally, and the application of **heat,** will be found to be helpful. After the painful stage has passed the neuritis should be treated as in the case of lead-palsy (*q. v.*).

Prognosis.—Chronic arsenic-poisoning is rarely fatal. The symptoms are usually severe enough to demand treatment before irreparable damage has been done. The palsies recover slowly, but usually, with proper treatment, completely. In neglected cases there may be permanent atrophy and contractures.

Pathology.—In chronic poisoning autopsies are rare. One would expect to find malnutrition and anemia, evidences of peripheral neuritis with atrophy of the muscles, and the characteristic skin lesions.

BIBLIOGRAPHY

BAILLY AND MACKAY. Arch. Int. Med., 1920, xxv, 628.
EDSALL. Modern medicine. Philadelphia, 1914, ii, 373.
PUTNAM. Boston Med. and Surg. Jour., 1889, cxx, 235.
——— Boston Med. and Surg. Jour., 1890, cxxii, 421.
SOLLMANN. Manual of pharmacology, Philadelphia, 1917.
THOMPSON. The occupational diseases, New York, 1914, Part iii, p. 162.

CHAPTER VI

FOOD-POISONING

By Seale Harris, M.D.

Definition, p. 89; Etiology, p. 91:—Exciting cause, p. 91:—Modes of conveyance of the organisms, p. 91—Causes other than specific organisms, p. 102; Food preservatives, p. 106; Food substitutes, p. 107; German literature on food-poisoning, p. 109—Food idiosyncrasies, p. 109; Symptomatology, p. 111:—Clinical history, p. 112:—Mode of onset, p. 112—Diagnosis, p. 114; Pathology, p. 115:—Bacteriological examinations in suspected cases of food-poisoning, p. 115—Treatment, p. 117:—Prophylaxis, p. 117; Symptomatic treatment, p. 117.

Synonyms.—Food intoxications; Food infections; Food-borne infections; and Poisoning from food adulteration.

Definition.—*Food-poisoning* is a general term commonly used to describe a condition resulting from the ingestion of animal or vegetable foods, which have become contaminated with bacteria or other microorganisms or with the toxins generated by bacterial action, to such an extent that they become pathogenic to human beings; or, it refers to the toxic symptoms that follow the use of food that is adulterated with, or contains as accidental impurities, mineral poisons which render it deleterious to health.

Food intoxication refers to the toxic symptoms that follow the use of food containing chemical poisons or toxins originating from bacterial action outside the body. Recent investigations have shown that the symptoms of what is ordinarily called "ptomain" poisoning more often result from bacterial action within the gastro-intestinal tract after the ingestion of contaminated food, than from the toxins formed before it is eaten.

Food infection is a term that might be restricted to the acute gastroenteritis associated with, or occurring without, general toxemia, which comes on within 48 hours after the ingestion of food contaminated with bacteria, or with other microörganisms. The manifestations of gastroenteritis subside without the appearance of symptoms of specific diseases of bacterial origin. In many cases it is not possible to draw a sharp line of distinction between food intoxications and food infections because both factors may be operative in the same patient.

Food-borne infection is the proper term for the illnesses resulting from the ingestion of food contaminated with the microörganisms causing infectious diseases like typhoid and paratyphoid fevers, diphtheria, scarlet fever, streptococcic sore throat, and other acute infections which produce definite symptoms. Ordinarily there is a period of incubation of at least several days from the time the microörganisms in the food are ingested before the onset of the attack in food-borne infections.

Poisoning from food adulteration is perhaps the most correct term to employ in the nomenclature of illness following the use of food that contains a mineral poison, present as an accidental impurity, or introduced as a preservative or to change the taste or appearance of the food, in such quantities that it becomes injurious to human beings. Poisons added to food with criminal intent are properly considered in treatises on toxicology.

Food-poisoning occurs very much more frequently than is generally supposed, although it is difficult to obtain any reliable data as to the frequency of its occurrence. There are many mild cases, in which infected food brings on symptoms like nausea and vomiting, or diarrhea, which usually subside without treatment. Such cases are not reported, and there are no reliable statistics on the subject. It is only when a number of persons become ill from eating infected or adulterated food, or when a severe case or a death occurs, that attention is called to the subject. Food-poisoning occurs most frequently in the summer, because the warm weather furnishes some of the conditions favorable to the development of bacteria, and of their toxins, which are usually responsible for the toxic symptoms that result from the ingestion of impure or infected food.

The mere fact that an attack of acute illness comes on soon after eating is enough to make the diagnosis of food-poisoning clear in the mind of the average person; and, according to the newspapers, one of the most frequent causes of sudden death is "ptomain poisoning." In reality many such cases are due to organic disease within the abdomen, which produces symptoms referable to the stomach and intestines.

The use of the term "ptomain poisoning" should be discontinued, because it has never been proved that ptomains have anything to do with the symptoms that occur as a result of eating poisonous food. Toxic ptomains are not found in meat until the late stages of putrefaction, when it is in such a condition that no one would eat it. Experiments on many different animals have proved that ptomains, or the products of the putrefaction of meat, are but slightly toxic, if poisonous at all; therefore, "ptomain poisoning," as well as "biliousness," and "congestion," should be relegated to the medical junk heap. "Acute indigestion" is often used as synonymous with food-poisoning. It is a meaningless term and should be discarded.

It would be well if public health authorities should decline to accept reports of "ptomain poisoning," and "acute indigestion," as causes of illness, or death. These terms are inaccurate, unscientific and misleading. The term "food intoxication," or "food infection," should be substituted, with a qualifying clause stating the kind of food bearing the microörganisms responsible for the symptoms, and the type of infection, if it is known.

Perhaps it would be best to discontinue the use of the term "food-poisoning'' except as a temporary diagnosis, until the type of infection or adulteration has been determined. It surely seems best to adopt the rational nomenclature and to name or classify diseases according to their etiology. It is unscientific to call a paratyphoid infection food-poisoning, because the bacilli causing this definite disease happen to be introduced into the gastro-intestinal tract with the food. The same is true of other food-borne infections, and of the mineral poisons which may be present as food impurities, or adulterations.

Food that is not in any way contaminated may cause serious symptoms in certain individuals who have an idiosyncrasy for certain articles of diet, such as milk, eggs, shell-fish, and berries. This idiosyncrasy is also known as ''food sensitization,'' or ''food allergy.''

The whole question of food-poisoning has received but little attention from the medical profession in general. The purpose of this discussion is to present some facts which may prove helpful to the medical practitioner in coming to a better understanding of the causes, symptoms, course, and treatment of the various kinds of food-poisoning.

Etiology.—EXCITING CAUSE.—*Modes of Conveyance of the Organisms.* —The articles of diet which are most frequently said to cause food-poisoning are: meats of all kinds; fish, oysters, and other shellfish; canned foods; milk, and its derivatives, such as cheese and ice cream; mushrooms and other poisonous plants that are mistaken for the edible varieties; fruits; uncooked vegetables, such as lettuce, watercress, and celery. The majority of the cases of food-poisoning with which the writer has had experience occurred from the use of meats, fish, oysters, and canned foods. In some cases the food was contaminated before it was brought into the home; in others, a part of the food was used at one meal, and the remainder kept one or several days before eating.

1. *Meat Infections.*—Meat, of various kinds, is the article of food under greatest suspicion of causing food-poisoning. It may be infected by disease while the animal is still alive, or it may become contaminated by flies, dust, unclean containers, or soiled hands after the animal is slaughtered. Meat is no doubt very frequently infected by careless handling. Many more cases of food-poisoning would occur were it not for the fortunate fact that the heat used in cooking meat destroys most bacteria and the toxins that are elaborated by them.

Meat is less liable to carry infection when thoroughly ''done'' than when it is cooked ''rare.'' Some of the pathogenic organisms in infected meat may be in the center of the roast, in meat pies, or other cooked meat dishes, and may not be destroyed by cooking. If such meat is kept for several days the bacteria in it propagate rapidly, and it becomes highly poisonous. Great care is, therefore, necessary in handling meat, to prevent infection, because people will continue to eat food prepared in the way they like it best even at the risk of becoming ill.

The ''stock pot'' in which meat soups have been left for several days has been the source of a number of reported cases of food-poisoning. Meat broth is a good culture medium for many pathogenic organisms, and the "stock pot," if not properly cared for, may become contaminated. In a day or two it may contain millions of bacteria, with the toxins that have been generated by them, thus becoming highly poisonous as food.

Food-poisoning is apparently much more frequent in countries where sausage, ham, and other meats are eaten raw. Bologna sausage and raw meat of various kinds are being consumed in increasing quantities in the United States. The latest fad is the "raw beef sandwich." Our health authorities should inform the public of the danger of eating raw meats, and thus prevent many cases of food-poisoning among those who are taking up raw meat fads, most of which originated in Germany. The heat from cooking, however, does not always destroy the toxins which cause food-poisoning. The toxins in the meat of animals that are infected with Gärtner's bacillus, which causes fever and diarrhea in cows and hogs, somewhat like "hog cholera," are not destroyed by heat.

The refrigeration of meat, as now practiced everywhere, since it inhibits bacterial growth, has no doubt decreased very materially the number of cases of food-poisoning. The cold storage of meat immediately after the animal has been slaughtered, and the general installation of refrigerators in hotels, cafés and homes, has no doubt prevented many cases of food infection. Judging from the information available, it appears that most cases of food-poisoning have occurred in homes in which there were no refrigerators.

Methylguanidin, a ptomain which has been isolated from spoiled meat, was for some time thought to be the toxic principle in meat-poisoning, but recent investigations prove that this ptomain may not be toxic to human beings. Spoiled meat which undergoes putrefaction by the ordinary saprophytic bacteria has been proved by experiments with animals not to be toxic, except in the late stages of decay when no one would eat it on account of its taste, odor, and appearance. It is, therefore, probable that putrefying meat may be eaten without danger to human beings. It is only when meat is infected with pathogenic bacteria that it causes food-poisoning. It should be remembered, however, that decaying meat may contain pathogenic bacteria in addition to the ordinary saprophytic organisms that cause putrefaction.

If spoiled meat contains pathogenic organisms, it is likely to be highly toxic, because the longer pathogenic organisms are allowed to grow on meat, the greater the number of bacteria and the more virulent their toxin.

The pathogenic bacteria, whose habitat is the intestines of man and animals, have been proved to be the source of infection in most cases of meat-poisoning. The *Bacillus enteritidis,* discovered by Gärtner, in 1894, has been isolated from the meat which caused a number of outbreaks of food infection. It resembles the colon bacillus in appearance and has many of the same cultural characteristics. It is pathogenic to cows and hogs as well as to human beings, producing in them an enteritis with fever, and other evidences of general toxemia. The enteritis in animals, due to the *Bacillus enteritidis,* closely resembles typhoid fever in man, and the animal thus infected may be a source of infection on account of its meat, which contains the organism, and through its feces, which may contaminate the meat if it is carelessly handled.

The *paratyphoid* group of bacteria is also regarded as one of the chief sources of meat infection. It is known that cows may become ill from paratyphoid infection, and it is probable that some of the cases of meat-poisoning result from eating beef that is derived from animals infected with paratyphoid fever before they are slaughtered. Human paratyphoid carriers are a source of infection. They may infect meat during its preparation. Since meat is a good culture medium for the paratyphoid group of organisms, if several days have elapsed from the time that it is infected until it is eaten, it becomes highly toxic, causing a severe gastro-enteritis, which may or may not be followed by a typical, or atypical, paratyphoid fever course.

Meat may be infected with the *Bacillus enteritidis,* or with the paratyphoid organism, or it may contain the toxins elaborated by these bacteria in such quantities that it is highly toxic, without its taste or appearance being affected. The difficulties of determining by an ordinary inspection of meat whether or not it is toxic are apparent. The temperature should be taken of every animal that is to be slaughtered, and if there is fever it should not be killed until it has been kept under observation for several days. It surely seems that the efficiency of meat inspection can be increased very greatly if all animals which are to be slaughtered for human consumption are kept under observation for several days by a competent veterinarian before they are passed upon as fit for human food.

Jordan,[1] in illustrating the difficulty of determining infection of the meat of animals after death, relates a case of a veterinary surgeon in Ghent, who was so convinced that the meat which he had inspected, and which was thought to be the cause of an outbreak of food-poisoning, was not contaminated, that he ate some of it. In a few hours he developed symptoms of severe infection from which he died in five days. Autopsy proved that the paratyphoid bacillus caused the infection.

Meat may carry the organisms and toxins of a number of specific diseases: *i.e.,* tuberculosis, typhoid fever, botulism. It may also harbor, and transmit, trichina (*Trichinella spiralis*), *Tænia saginata* (beef-tapeworm), *Tænia echinococcus,* and other animal parasites that are pathogenic to man.

2. *Fish Infection.*—Fish-poisoning, "ichthyotoxism," is of frequent occurrence. It may originate from a piscine disease with which the fish was infected during its life, but, generally speaking, fish-poisoning results from contamination by fishermen, fish dealers, cooks and others who handle the fish from the time they are caught until they are served for eating. It is undoubtedly true that fish are susceptible to epidemics which destroy great numbers of them, and unscrupulous fishermen have been known to sell fish that have died in piscine epidemics. The char-

acter of the diseases which may infect fish is not thoroughly known, but in one epidemic an organism very closely resembling the *Proteus vulgaris* has been found in fish that died of disease.

Fish that grow in polluted waters may become infected with a number of pathogenic organisms, and these organisms and their toxins may produce symptoms of food-poisoning. The proteus bacillus, the paratyphoid bacillus, the colon bacillus, and the *Bacillus enteritidis,* have all been found in fish. Brieger has isolated the *Bacillus botulinus,* and the poisonous alkaloid, mytilotoxin, from decaying fish.

It has been noted that the flesh of some fish is quite wholesome at times, and poisonous at other times. It is said that the bluefish, which is quite generally used for food, may become poisonous, if it happens to feed upon the poisonous "mossbunker," sometimes used as bait by commercial fishermen. The alkaloids contained in the mossbunker are thought to permeate the meat of the fish to such an extent that it becomes poisonous even after cooking.[2] It is stated that the sturgeon, pike and other fish are not poisonous except during the spawning season. At such times their roe and flesh may be mildly toxic.

A number of fish in foreign waters are normally poisonous to human beings. The blowfish, or *Tetraodon hispidus,* found in the waters of Hawaii, are said to be quite poisonous, being called "muki-muki," or "deadly death," by the natives. The "fugu" fish in Japanese waters are reported to have caused many deaths. The "puffers" and "balloon" fish belong to the poisonous varieties. The fish which are considered normally poisonous are most frequently found in tropical countries, where the water is warm. This seems to indicate that the poisonous quality results from toxins due to bacteria that are ingested by the fish either with marine plants or with animals. Clark,[3] of the United States National Museum, states that the flesh of the Greenland shark has produced poison, although the flesh of other sharks is quite harmless.

Fish caught with a hook and allowed to die very slowly are said to decay more rapidly than those killed immediately after they are caught. It is a law in Europe that fish caught with a hook or net must be killed immediately, just as beef is butchered.

It has been found that the more thoroughly fish is cooked the less danger there is from eating it, because heat destroys bacterial toxins. However, some of the toxins that are found in the flesh of fish withstand prolonged boiling.

Canned fish, particularly canned salmon, has been thought to be the cause of a number of cases of so-called "ptomain poisoning." This is most apt to occur when the cans have been opened and a part of the contents used for one meal and the remainder kept for a day or two before being served. Heat destroys most of the toxins with which fish is liable to become contaminated, and it is therefore advisable to cook it thoroughly, particularly if it is not known to be perfectly fresh. It is safest to cook canned salmon and other canned or preserved fish before it is eaten.

3. *Oyster and Shellfish Infections.*—Many outbreaks of food-poison-

ing have been reported from eating infected oysters, and a great many more mild cases occur that never come under the observation of physicians. It is a common thing to hear persons say that at some time in their lives they have been ill from eating oysters. When one thinks that the source of our oyster supply is known to be the polluted, brackish water near the sewer outlets of cities, and when the fact is considered that millions of people eat oysters every year, it is surprising that there are not many more cases of food-poisoning from this source.

A number of epidemics of typhoid and paratyphoid fever have been traced to oysters, and no doubt many thousand cases occurring each year originate from this source, although they cannot be traced directly. The fact that the great majority of adults have had typhoid fever, and are, therefore, immune to the disease, is another reason why more cases do not occur from eating raw oysters, a food that is so liable to contamination with the typhoid bacillus.

The intestine of the oyster is filled with microörganisms which have been taken in from the water in which oyster beds are planted, and the brackish water on which they fatten is often polluted with pathogenic bacteria. The oyster decomposes quickly, and the paratyphoid, typhoid, and other bacteria that live in water, in addition to the ordinary germs of putrefaction, find it a good culture medium. There is no question that the oysters grown in polluted waters take in and retain pathogenic organisms.

It is doubtful whether there are any oyster beds close enough to cities to be successful commercially that are not contaminated. On the basis of information collected from bacteriological investigations of the oyster beds in various parts of the country, the entire shellfish supply of the United States is under suspicion, but as yet little has been done to protect the oyster beds from sewage pollution. The Government, however, is making efforts in this direction, having stopped to some extent the "fattening" of oysters in polluted waters. With an increasing population the difficulties of preventing the pollution of oyster beds will become greater, and the outlook for a clean and uninfected oyster supply is not encouraging. Many people who are informed regarding the source of the oysters obtainable in cities have given up the delights of the delicious flavor of raw oysters because of their fear of infection.

G. A. Johnson,[4] of the New York City Board of Health, who has made a special study of the oyster beds around New York, says: "There is no body of water extant that has produced so many cases of typhoid in human beings as . . . . Long Island Sound. A good second is lower New York Bay, reeking in sewage and pollution from factories. It is a crime to allow bivalves from such sources to be sold in the markets."

Since oysters are eaten raw, and since they are so apt to be contaminated, there is probably more risk in eating them than in eating most other foods. It has been proved that cooking oysters does not destroy all the germs or toxins which they contain, but undoubtedly cooked oysters are safer for human consumption than are the succulent bivalves when eaten raw.

In a report on the sanitary conditions of the Rhode Island oyster beds, Gorham,[5] of Brown University, states that bacteriological examinations of oysters made in summer did not agree with those made in the same bed in winter. He observed that the number of colon bacilli in the oysters increased from spring to the end of summer, reaching its maximum when the water was warmest, at which time practically every oyster showed numerous colon bacilli in 1/100 c.c. of "shell water." These observations afford a scientific explanation for the belief that oysters should not be eaten in summer, because of the greater danger of infection during the warm weather. Gorham suggests that four of the "R" months, "March, April, September, October," ought to be added to the season when oysters should not be eaten.

The foregoing statements regarding the polluted sources of oysters and the infections which they may carry, applies to mussels, crabs, shrimps, lobsters, and other shellfish that grow in brackish water. The flesh of crabs, being soft, decomposes readily and is very liable to bacterial infection. It is, therefore, very important that crab meat should be fresh and well cooked before it is eaten. The same is true of shrimps, but to a lesser extent. Lobster is ordinarily considered very indigestible. It is probably no more so than other meats. The fact that lobster so frequently causes indigestion is not because of the character of lobster meat, but probably because there is such frequent opportunity for infection.

There is a popular belief that the combination of fish and shellfish with milk is poisonous. There is no foundation for this fallacy. It is probably due to the fact that fish, shellfish, and milk, are all very liable to contamination. One or the other causes the gastro-intestinal symptoms ascribed to the combination, or to an idiosyncrasy for one or the other. Some years ago, in Mobile, the writer was one of a group of eight or ten men who ate at the same place for several months. Fish, crabs, shrimp, or oysters were served every day. The person who selected them was trustworthy. There was also a liberal supply of pure milk, cream, and buttermilk. All kinds of fish and shellfish were eaten at the same meal at which sweet milk and buttermilk were copiously indulged in. All of the party remained perfectly well throughout several months of a hot summer.

4. *Infection from Canned Foods.*—Canned foods are thought to be a frequent source of food-poisoning, but it is probable that with modern methods of canning there are comparatively few cases in which canned or preserved foods carry infection, or are toxic in any way.

During the years of the war the United States Army consumed enormous quantities of canned foods—meats, vegetables, and fruits. The fact that there were so few cases of food-poisoning among 4,000,000 soldiers indicates that the danger from eating canned foods is so very slight as to be considered almost negligible. Most of the cases which the author has known in which canned foods have been thought to be a source of infection were cases in which the food probably became infected after the cans had been opened. The usual history in such cases is that a can containing food was opened and part of its contents used one day, and the remainder, which meanwhile had an opportunity to become infected, was eaten a day or two later.

With modern methods of canning meat, vegetables and fruits, in which the cans and other containers are hermetically sealed, there is little likelihood of infection. If fermentation or putrefaction takes place, gases are usually formed and the can or other container of food is likely to be cracked, or "blown," at least to the extent of allowing the gases to escape. If the container of canned, or preserved, foods is not hermetically sealed it is liable to infection. It is, therefore, safest not to eat food which has remained for any length of time in a can or jar in which there is a leak or break of any kind.

It is a fact, however, that infection from canned or preserved food does occur. It is not the fault of the method but of the carelessness of the persons engaged in the work of canning and preserving food. It was formerly thought that the food contained in cans would take up enough tin to cause toxic symptoms; but it has been proved that tin, in the quantities which can be dissolved and absorbed by food, cannot cause symptoms of poisoning. The use of canned and preserved foods is of great value for the nutrition of enlightened people, but manufacturers of canned and preserved foods should teach their employees that carelessness in their methods may cause many deaths.

The home canning and preserving of vegetables and fruits is a movement that is making farming and gardening a much more profitable and healthful occupation than it was in the past; but the amateurs in food preserving should be made to realize the danger from the careless or improper handling and preparing of foods, as carelessness may affect both their families and the purchasers of their products. Nine-tenths of the work in preventing disease consists in education. The medical profession and public health authorities should see to it that the public is informed regarding the proper selection, handling, preparation, and care of food intended for human consumption.

5. *Milk Infections.*—Since milk is a good culture medium for many pathogenic bacteria, and since the way in which it is handled renders it very easy of contamination, this important article of food is frequently infected, and is a source of many acute illnesses, particularly during the summer months. The pathogenic microörganisms that are carried by milk may be derived from an animal infected with bovine disease. but more frequently milk is contaminated in handling.

Cows may have diarrhea due to the *Bacillus enteritidis,* which is the organism responsible for the many outbreaks of food-poisoning. This bacillus may be in the milk of an infected cow, or it may come from the feces which soil the udders and thence are transmitted to the milk, if the udders are not carefully washed before milking. Cows are also known to have been infected with the paratyphoid bacilli, and they may be "carriers" of the *Bacillus enteritidis,* the *Bacillus paratyphosus* and other bacteria which are pathogenic to human beings. The milk from animals which have puerperal or other forms of septicemias, and from cows having local streptococcic or staphylococcic infections of the udder may produce gastro-enteritis in adults as well as in children. Cows may also be afflicted with tuberculosis, anthrax, foot and mouth disease, actinomycosis, and may transmit, through their milk, these and other diseases that infect man and animals.

Milk, however, is most frequently infected from outside sources, and the human carriers of *Bacillus coli communis*, *Bacillus typhosus*, *Bacillus paratyphosus*, *Bacillus enteritidis*, *Bacillus dysenteriæ*, streptococcus, and other microörganisms are generally responsible for the infection of milk. The infection causing summer diarrhea in infants and outbreaks of bacillary dysentery among adults is usually of one of the above types.

Flies, dust, unclean milk vessels, and unclean hands on the part of the milker and of others who handle milk and its products are the usual sources of infection. Milk that is fresh from the cow, if properly handled by certified milk producers, contains very few microörganisms, and if kept cold will be pure and wholesome for days, whereas, milk that is handled by dirty and careless milkers, and placed in unclean vessels, and is not kept cold, becomes seething with bacteria in a few hours. If pathogenic microörganisms happen to be present, it becomes poisonous to the consumer. Milk infections are much more frequent in summer than in winter for the reason that the pathogenic bacteria propagate best in warm weather.

The majority of cases of milk infections show the symptoms of a gastro-enteritis, usually vomiting and diarrhea, but in some cases, particularly in infants, there is a high degree of toxemia, characterized by high fever, convulsions, or stupor, coma, and death.

Milk is the vehicle for carrying a number of infections to man. Among them are typhoid fever, scarlet fever, diphtheria, and streptococcic sore throat.

The pasteurization of milk destroys most of the pathogenic bacteria and their toxins with which it may become contaminated. This fact is so well known that many cities have installed pasteurization plants in which all milk is pasteurized before it may be sold. In the cities requiring pasteurization of milk, a reduction in the typhoid and the general infantile death rates has uniformly followed. It is, of course, possible, and even likely, that milk may become infected after it has been pasteurized. It is, therefore, best, particularly in hot weather, to pasteurize the milk at home before it is used. Pasteurization is said to destroy some of the vitamins in milk, but they can be supplied in fruit and vegetables, and it is better to risk nutritional disorders than the infections that so frequently follow the use of raw milk.

6. *Ice Cream Infections.*—Many outbreaks of poisoning have been traced to ice cream. It was formerly thought that tyrotoxicon, which is formed in ice cream that has been allowed to melt and has been kept in tin freezers, was the active toxic principle in ice cream poisoning; but it

is now known that the toxic symptoms that follow the use of ice cream are due to the pathogenic bacteria which contaminate milk. Freezing does not destroy the colon bacilli and allied group of organisms which pollute milk, and since the milk that is used in the manufacture of ice cream is sweetened and flavored, it is often not kept as carefully as is milk intended for drinking. It is, therefore, more likely to contain a larger number of bacteria, with more concentrated toxins, than fresh milk. In recent years, particularly in the cities, the public health authorities have required ice cream manufacturers to pasteurize their milk and to be as careful in handling it as if they were milk dealers.

An epidemic of typhoid fever that occurred in Birmingham, Alabama, in 1915, was definitely traced to infected ice cream. It was thoroughly studied by Dr. L. L. Lumsden, of the United States Public Health Service. In this epidemic there were more than 1,000 cases, many of whom gave a history of eating ice cream. On inquiry it was found that a large number had purchased the ice cream from retailers who patronized one large ice cream establishment. Outbreaks of typhoid also occurred in several towns near Birmingham among the customers of retail dealers who purchased ice cream from the Birmingham wholesaler. An investigation of the ice cream plant, and the source of its milk supply, proved unmistakably that the source of infection in more than 1,000 cases of typhoid fever was ice cream. The epidemic subsided when this large ice cream factory was made sanitary and after the city government required ice cream dealers to pasteurize the milk used in the manufacture of ice cream.

7. *Cheese Infections.*—Cheese may retain infections that were in the milk from which it was made; but such instances are probably rare. It is possible that the bacteria to which cheese owes its taste, odor, and color, are antagonistic to most of the pathogenic bacteria that contaminate milk; and it is probable that in some cases the toxic symptoms which frequently follow the use of "ripe" cheese are due to the mycelium (mold) and perhaps to its toxins, which are present in cheese. There have been a number of cases of gastritis reported in which the mycelium has been known to live and propagate for months. It is entirely possible, however, that cheese may be contaminated with the same organisms which are responsible for outbreaks of food-poisoning from other sources. Considering the manner in which cheese is made, kept, and served, and the opportunities for infection, it is remarkable that more cases of cheese-poisoning have not been reported.

8. *Vegetable Infections.*—Few plants normally contain poisons, but there are some which are poisonous and which may be mistaken for the edible varieties. Chestnut[6] gives a list of about 30 poisonous plants, but some of these are not poisonous to man.

Certain vegetables, which are normally wholesome, like potatoes, may become poisonous under certain conditions, as in sprouting. It is probable that many of the cases of poisoning that have been reported from eating vegetables resulted from bacterial infection. This is true of the outbreaks of diarrheal diseases, and of typhoid fever, that have followed the use of celery, lettuce, watercress, and other uncooked vegetables.

Vegetables that are to be eaten raw become dangerous for consumption if grown in soil that is polluted either by the excreta that is washed out by rains from open privies, or by the use of feces, either from cattle, or from human beings, as fertilizers. Recent investigations indicate that the principal type of organism in food-poisoning, the *Bacillus enteritidis* of Gärtner, comes from the feces of cattle. Food inspection, to be effective in the case of vegetables that are to be eaten raw, should begin at the farm where they are produced.

Dairies in the country are inspected by the health authorities. Why should not farms on which vegetables to be eaten raw, like celery, lettuce, and berries, strawberries particularly, that are sold on the markets, undergo the same thorough inspection? The danger of infection from vegetables is not so great as from milk, because the latter is a good culture medium for many pathogenic bacteria, but human "carriers" may infect vegetables and fruits. Persons who handle food of any kind should be examined, to determine whether or not they are "carriers" of disease, just as is done with those who are engaged in dairying. If the city markets, and places where fruits and vegetables are sold, were required to be kept as sanitary as the dairies and milk depots, there would be fewer cases of food infection. It is the usual thing to see vegetables, fruit, and berries displayed in markets and on the street, where they are exposed to infection from flies, dust, and polluted water, and to handling by "carriers."

Decomposing vegetables are more apt to be infected than fresh ones for the reason that they have had a longer time to become contaminated, and if contaminated with pathogenic bacteria the latter have had a longer time to develop and elaborate their toxins. It is probable that decayed vegetables in themselves are not toxic to man, but the evidence of decay is a good index as to the opportunities for infection.

Potato-poisoning is perhaps of more frequent occurrence than is generally supposed. In the agricultural districts "new" potatoes and those that are old and "sprouting" are thought to be frequent sources of food-poisoning. The toxic principle in potato-poisoning is said to be solanin. In the outbreak in Glasgow, Scotland, in November, 1917, which was studied by Wright, Harris, and Cockburn,[7] solanin was found to be present in the sprouting potatoes in four or five times the quantity that occurs in potatoes normally. There were 61 cases with one death in this outbreak of potato-poisoning. The symptoms in this, as in other outbreaks, were those of a gastro-enteritis, *i. e.*, vomiting, diarrhea, colicky pains, headache, slight fever, and prostration. Jaundice and partial paralysis occurred in some of the cases. While solanin is no doubt the cause of most cases of potato-poisoning, potatoes that have been cooked for one meal and left over and served cold several days later, as in potato salad, may become infected and cause poisoning.

Tomatoes have also been under the suspicion of being poisonous. The writer recalls that fifteen years ago a Chicago physician reported a number of cases of functional cardiac disorder which he called "lycopercicum cardopathia" caused by eating over-ripe tomatoes. It has not been more than fifty years since tomatoes were first used for eating purposes, there having been a popular superstition that they were poisonous. There can be no doubt that tomatoes are wholesome, but since they are eaten raw and exposed to the dust in markets, and usually handled by various persons before they are served, they may carry infection. While thorough washing of tomatoes will not sterilize them, it will no doubt reduce the number of bacteria, and in the production of food-poisoning the dosage of microörganisms has a bearing on the severity of the symptoms. Tomatoes should be peeled before using. The tough skin is difficult to digest and also, when it is removed, the chances of infection from that source are reduced.

9. *Botulism.*—Botulism is usually classed under food-poisoning, but in reality it is a definite disease entity caused by a specific microorganism, the *Bacillus botulinus,* which was discovered by Van Ermingen, in 1896. Botulism, like typhoid fever and other infectious diseases, runs a definite course, with characteristic symptoms. It is a food-borne intoxication, inasmuch as the toxin generated by the *Bacillus botulinus* is transmitted to man on food, generally meat; but it is entirely possible that it may be conveyed into the gastro-intestinal tract in water, and perhaps in other ways.

The first cases of botulism were reported from Germany and they were so closely related to eating sausage, that the disease was called "sausage-poisoning." The term botulism comes from the Latin word botulus, a sausage. There have been a number of outbreaks of botulism in various parts of the world, but more cases have been reported from Germany and Russia than from other countries. There is no question that the disease exists in the United States, a number of cases having been reported from several widely separated cities in a number of states. The probable reason that less botulism has been reported in the United States than in the European countries is that we consume less raw meat.

The *Bacillus botulinus* is large, with rounded ends, one of the ends having a spore formation. It is an anaërobic saprophyte which grows best at room temperature. The *Bacillus botulinus* and its spores do not resist the heat used in cooking food, even very slightly. It does not thrive at body temperature and is killed by a temperature of from 140° to 158° F.[8] (60° to 70° C.). It grows well in meat-broth cultures and has been isolated from ham, sausage, and other raw meats. It has also been found on beans and other vegetables.

The fact that the period of incubation, or the prodromal period in botulism, is only from 24 to 48 hours, and the life history of the *Bacillus botulinus,* in so far as it is known, seem to indicate that the disease is due to a toxin which is formed in food outside of the body, rather than to poisons which are formed within the stomach or intestines after the ingestion of the food which carries the infection. Experiments on animals seem to prove that the *Bacillus botulinus,* like the *Bacillus tetani,* produces a true exotoxin, so that there is the hope of producing an antitoxin for botulism which will be as effective as that manufactured for diphtheria and tetanus.

The *symptoms* of botulism are probably due to degenerative changes in the central nervous system, particularly in the motor cells of the medulla and spinal cord. There may be no symptoms referable to the digestive tract; however, in some cases there is anorexia, abdominal discomfort, nausea and vomiting. Constipation is the rule, although diarrhea has been reported.

It is from the nervous symptoms that the diagnosis of botulism is made. The first symptoms of which the patient infected with botulism is likely to complain are a feeling of being tired, and difficult or double vision (nystagmus). There is vertigo both when standing and upon lying down. There may be some difficulty in swallowing, with dryness of the throat (thirst). The temperature is subnormal and there is no increase in pulse-rate.

After two or three days there may be ptosis of the eyelids, and paresis of the muscles of the throat may render swallowing difficult, or impossible. Later the paralysis usually affects the facial muscles, the muscles of the neck, shoulders, and arms, and there may be complete paralysis before death. Prostration occurs in the first few days and may increase rapidly. The urine becomes scanty and may finally be completely suppressed. The muscles of respiration are affected, there is difficulty in breathing, and finally death may come from respiratory paralysis. Pneumonia is a complication that may cause death in botulism.

The *mortality* of botulism is high, ranging from 40 to 60 per cent. The cases that recover are long drawn out, the paralysis of the muscles affected lasting for weeks or months.

In the *treatment* of botulism it is important to empty the stomach as soon as the first symptoms come on, because in this condition the stomach has been known to retain food for several days. **Gastric lavage** is the best method. A rapidly acting **cathartic** such as **magnesium sulphate,** 1 ounce (31.10 grams), or even **croton oil,** 1 to 2 drops, should be given as soon as the stomach is cleared out. After this is done the treatment is symptomatic and supportive. **Strychnin** is indicated as a muscular stimulant, and **camphor in oil** may be given hypodermatically as a general diffusible stimulant. It is important to give **as much food as can be assimilated** to support the patient until the effects of the toxin have passed off. Since there is paresis of the muscles of deglutition, it is sometimes necessary to feed the patient through a stomach or duodenal tube, or per rectum.

CAUSES OTHER THAN SPECIFIC ORGANISMS.—*Poisonous Plants.*—The principal danger from plants that are normally poisonous comes from the fact that they may be mistaken for edible varieties, which they sometimes resemble very closely. The roots of the *water hemlock* (*Cicuta maculata*) are very poisonous, and are sometimes mistaken for horseradish, artichokes, and parsnips. A number of deaths from such mistakes are reported every year.

Mushroom-poisoning is of much more frequent occurrence in Europe than in America, because the mushroom is considered a great delicacy on the continent and is eaten more by the Europeans than by Americans. Mushrooms, however, are being eaten more than formerly and since there are a number of the poisonous varieties of mushroom that are indigenous to various parts of the United States, we may expect more cases of poisoning from this source.

It is customary for authors to describe the differential points between the edible and the poisonous varieties of mushroom. The writer is of the opinion that the selection of mushrooms for eating purposes should be left to experts. Since he witnessed the autopsies on four individuals who had died as a result of their inability to discriminate between a mushroom and a toad-stool, he realizes the danger from eating mushrooms, and since then he has not been able to eat this delicacy with the same degree of relish as formerly.

Mushrooms have little food value, and since more cases of mushroom-poisoning are being reported every year, it seems that the eating of this fungus that grows in dark places should be discouraged. Even if there is only one case of poisoning to every 100,000 who eat mushrooms every year, since it is not an essential food or even a very nutritious one, the 100,000 can afford to do without an occasional article of diet to save even one life. Jordan[9] states that "in the vicinity of New York there were 22 deaths from mushroom-poisoning in one ten-day period in September, 1911." Jordan also reports the death of Count de Vecchi, an attaché of the Italian Legation in Washington, "considered something of an expert on mycology," who died from eating mushrooms which he himself had selected from one of the Washington markets.

The edible variety of mushrooms, the *Aminita cesaria*, is indigenous to the United States and it is also grown to a small extent for marketing in this country; but most of our supply is canned and comes from France, where it is grown in caves and other dark, damp places. The poisonous varieties of this fungus are the *Aminita muscurari* and the *Aminita phalloides* (death cup). They contain an alkaloidal substance, *muscarin*, a violent poison, which is responsible for the illness. Muscarin is said to produce hemolysis, which probably accounts for some of the symptoms.

The symptoms of mushroom-poisoning usually come on four or five hours after eating, though the time of onset may be a few minutes after the ingestion of the mushrooms. In some cases there is a prodromal period of fifteen hours. The first symptoms are usually abdominal discomfort which soon increases to intense pains, with violent retching and vomiting, diarrhea, and sometimes bloody stools. Prostration is extreme, the skin is icteric, cold and clammy, and there is a rapid loss of flesh. Drowsiness followed by coma and death in from four to five days is the usual course, although recovery from mushroom-poisoning has been known, when small quantities were eaten, and the stomach promptly emptied.

The *pathological findings* in mushroom-poisoning are much like those of acute yellow atrophy of the liver. The autopsies which the writer saw showed a marked reduction in the size of the liver, with extensive fatty changes in the liver, kidneys and myocardium.

In the *treatment* of mushroom-poisoning the most important indication is to **empty the stomach,** if possible, before the poison gets into the intestines. **Lavage** is the best method. If the condition is not discovered within five or six hours from the time of the ingestion of the mushrooms there is very little hope from any form of treatment. **Atropin** is the physiological antidote for muscarin and should be given in large doses, 1/50 grain or even 1/25 grain, until the physiological effect is produced. Since the hemolysis is probably the most important change in mushroom-poisoning, it may be that transfusion, or the intravenous use of a normal saline or alkaline solution would be helpful.

Chemical Impurities in Food.—Poisoning from accidental chemical impurities in food was formerly thought to be frequent, but bacteriological studies in many outbreaks of food-poisoning have proved that these were due to infections, and it is now believed that acute poisoning from chemicals, whether organic or mineral substances, in food, is extremely rare. It may, however, occur in cases of gross carelessness in handling and preparing foods which are liable to contamination by various organic and mineral substances.

It is true that many foods may contain small quantities of chemical substances which, while not enough to cause acute toxic symptoms, may, by their cumulative action, produce symptoms of chronic poisoning. It has been suggested that one of the causes for the increase in the degenerative diseases (chronic cardiovascular-renal diseases), is the daily use for years of foods containing accidental impurities of various kinds. This is a theory which cannot be verified by experiment, but it is surely safest to be informed regarding the chemicals that are used as food preservatives or adulterants, and those which may occur as accidental impurities in many articles used in our daily diet.

Various organic and mineral poisons may form accidental impurities in food. They usually occur in the manufacture of cheap food preservatives, or food substitutes, or get into food through gross carelessness on the part of those handling it. These chemicals, when accidentally introduced into the stomach in food, cause the characteristic symptoms of the particular mineral poison in question.

Arsenic is one of the most important chemical impurities which may poison food. Arsenic is an impurity in iron pyrites, employed in the manufacture of sulphuric acid, which is constantly used in the production of glucose.

Glucose is one of the most largely used food adulterants, being sweeter and cheaper than sugar. It is one of the important ingredients in candies, syrups, preserves, and other sweets that are sold on the market. Since these foods are used so largely by children, it is important that they contain no impurities that can be harmful. Arsenic is frequently found in glucose that has been made of cheap and impure sulphuric acid.

Glucose is also used in the manufacture of beer and likewise no doubt in the production of the cheap beer substitutes now on the market. It would seem advisable to carefully investigate the industries that manufacture glucose, and those in which it is employed in making foods and drinks for human consumption. There is no way of investigating the harmfulness of the daily ingestion of small quantities of arsenic, yet it cannot be considered wholesome.

That there is danger in the use of glucose containing arsenic as an impurity is evidenced by an epidemic of "multiple neuritis" in the English Midlands in 1900. About 6000 persons were affected and there were about 70 deaths. The source of this outbreak of chronic arsenical poisoning was traced to arsenic in beer, in the brewing of which cheap sugar, containing arsenic as an impurity, was used.

Lead-poisoning is said to be due more to the ingestion of food that is handled by painters in eating, than to the absorption of it through the skin. Lead-poisoning has also been known to occur from the continued use of beverages sold in bottles with lead stoppers. This, however, must be a very infrequent source of lead-poisoning. Enormous quantities of chocolate candies, that were wrapped in foil, were consumed by the American soldiers in France, but no case of lead-poisoning was reported. *Lead chromate* was formerly used in coloring candies yellow. It is a practice that should be discouraged, for undoubtedly if lead chromate is used very much chronic lead-poisoning will result.

The lead used in soldering canned foods has been under suspicion, but there is probably not the slightest chance of chronic lead intoxication from this source. It is possible that the constant use of drinking water that has passed through lead pipes is a source of danger. Lead pipes, therefore, should not be used in the plumbing of fixtures or on hydrants from which drinking water is procured.

Copper compounds have been held for many years to be among the chemical poisons which may contaminate food. *Verdigris,* or *copper acetate,* a poison said to be formed in copper cooking utensils in which food is allowed to stand too long, was feared by every educated housewife, a few decades ago. It is now believed that the cases of poisoning formerly attributed to verdigris were really food infections.

Copper sulphate, said to be used by the French and other European manufacturers to reproduce the green color of peas, beans, and other green vegetables, is a highly poisonous compound. It is claimed by the manufacturers that they do not use the copper sulphate but other salts of copper which are not so poisonous. It should be said to the credit of American canners that they do not use copper salts for coloring peas, and other green vegetables,[10] and the United States Government has prohibited the importation of peas and other vegetables which have been colored with copper salts.

Tin was under suspicion for a long time as a source of poison in canned foods. Traces of tin are frequently found in canned foods, but there is no evidence to prove that it is the cause of acute food-poisoning, and nothing is known of any cumulative action of tin. However, tin or any other mineral, as an impurity of food, cannot be regarded as wholesome. If upon opening a can of food the tin appears corroded it is likely that its contents have dissolved some of the salts of tin. For the same reason food in old and rusted cans should not be used unless one is absolutely sure that it is pure and wholesome.

FOOD PRESERVATIVES.—The use of chemicals for preserving food has been a matter of heated controversy for a number of years. Their value would depend upon their antiseptic action, and whether chemicals strong enough to destroy bacteria, or to inhibit their growth in food, would not be deleterious to the protoplasm of the cells of human beings, is still a debatable question.

Benzoate of soda as a food preservative is a subject of much discussion. Dr. Harvey W. Wiley maintains that it interferes with metabolism, and that its use disturbs digestion and is deleterious to health. Dr. Wiley made some investigations with what he called "poison squads," which proved, to his satisfaction, that benzoate of soda should not be used as a food preservative. A number of other experiments to determine the toxicity of benzoic acid and the benzoates have been carried out, which seem to indicate that it would require large doses used over a long period of time to act injuriously in the human body.

Benzoic acid is normally found in considerable quantities in many fruits and berries, particularly in cranberries, and the human body is able to appropriate considerable quantities, which are converted into harmless hippuric acid. It therefore seems probable that the ingestion of small quantities of benzoate of soda in conjunction with food may not be injurious, yet the matter is open to question, and it seems safest not to use foods that have been preserved with benzoic acid.

Boric acid and *borax* are also used for preserving foods, but when used in sufficient quantities to preserve food they are surely injurious to human beings, and should not be used.

The more powerful antiseptics, *formaldehyd, salicylic acid,* and *sulphuric acid,* were formerly used by unscrupulous manufacturers in preserving foods, but since the Government has condemned their use, this danger is now rarely encountered.

The safest methods of preserving food are, (1) *heat,* (2) *dehydration,* and (3) *refrigeration.* Sterilization by heat of fruits, vegetables, and meats that are preserved in sealed containers, is surely safer than the use of chemicals as preservatives, even of those which are considered harmless.

It has been known for ages that fruits, vegetables, and meats which have been "dried," keep well and are fit for food for months or years. Formerly this drying process was done by sunlight, or by crude methods of drying in "smoke-houses." We now know that food "spoils" and becomes toxic to human beings because of bacterial infection, and that the drying process makes food an unsuitable culture medium for germs, which require moisture for their growth and development. It should be mentioned that in the preservation of meats by smoking, they become impregnated with creosote, which is an irritant poison if used in large quantities. It is probable, therefore, that the creosote in "smoked" meats is more toxic than the benzoate of soda used in "embalming" beef.

Methods of dehydrating vegetables and fruits have recently been perfected whereby they may be preserved, and kept indefinitely. Upon the addition of water, they have much their normal flavor and appearance. Vegetables and fruits preserved by dehydration also have the advantage of being light and compact, so that they take up but little space in shipping. This was of enormous importance in the World War, when space was so urgently needed for shipping soldiers and food to France and other European countries. Large quantities of dehydrated vegetables were consumed by our soldiers both in this country and in France, and the general opinion is that the preservation of vegetables by dehydration is an improvement over former methods.

Among the great advances that add to the comfort of life are the improvements in the refrigeration of foods, whereby the markets in every city have on hand at all seasons of the year a bountiful supply of all kinds of fresh meats, fruits, and vegetables. There is no question that foods kept cold retain their taste and appearance (palatability) better than those preserved in any other way. Refrigeration, however, is the most expensive way of preserving food, and, as in other methods, the safety of refrigerated foods depends upon the eternal vigilance of the persons who carry out the process.

The greatest care should be used in handling refrigerated foods because, while cold inhibits bacterial growth, it does not destroy the microorganisms implicated in food-poisoning. If food is infected before it is placed in a refrigerator, it will be toxic for months afterwards. Refrigerators may become infected and, therefore, should be kept scrupulously clean.

Food Substitutes.—During the World War, when there was a scarcity of food in every country in the world except the United States, a number of substitutes for various foods were quite generally used. It is probable that because of their cheapness some of these food substitutes may continue in use in European countries and that they may be introduced into the United States.

Saccharin was used every day for two or three years by millions of French, British, and Italians, who were deprived of the use of sugar by the exigencies of war. Saccharin was not only used in sweetening coffee, tea, and cocoa, but it was employed, to a large extent, in the manufacture of jams, jellies, and preserves, which were the only forms of sweets obtainable in many parts of France, England, and Italy. Saccharin is a coal-tar product, and being 280 times sweeter than sugar, it will probably always be more economical than sugar. It is, therefore, likely to come into general use by the manufacturers of sweets in the United States.

Whether or not the continued use of large quantities of saccharin is harmful is yet to be determined. Apparently saccharin in the quantities used in food is not likely to produce acute poisoning, but the cumulative effect of this coal-tar derivative should be investigated. The U. S. Department of Agriculture[11] is authority for the opinion that saccharin in food for normal persons is undesirable and perhaps harmful.

Butter substitutes are being used quite extensively and, with the increasing price of this food, which is generally considered indispensable, it is probable that many vegetable fats will be added to those now in use. That a few of the vegetable fats are poisonous is certain, and it is possible that some of them may be placed on the market before their poisonous properties are recognized. Jordan[12] mentions an outbreak of food-poisoning in Hamburg and a number of other German cities in which a butter substitute, *"maratti-oil,"* caused several hundred cases of illness. This "maratti-oil," derived from a tropical plant (Hydrocarpus), was proved to be toxic to animals. The Germans have suffered more from the lack of fats than from the lack of any other article of food. In February, 1918, only 50 grams of margarine were allowed to each adult in Germany every ten days, and they are using fats from every available source as substitutes for butter and lard. It may be that we shall learn of other poisonous oils from the Germans.

The Germans now use "egg powder," "milk powder," "meat powder," and other substitutes for the foods of which they were deprived by the British blockade of their ports. These substitutes were said to have been made largely of synthetic chemical products. The Germans were also deprived of the use of fruit juices, having had no oranges, lemons, or other tropical fruits for four years. They used synthetic acids instead, and we may expect, when our markets are open to the Germans, that the manufacturers of soda water and other soft drinks, which are so extensively used in the United States, will take up these substitutes even more than is now the case.

Soft drinks have become so much a part of the food and drink of millions of persons, that their composition and physiological effects should be thoroughly investigated. Many of them contain saccharin, and artificial acids and other chemicals which may be as harmful as benzoate of soda and other preservatives of meats which have been condemned by many food experts. *Saponin,* a chemical which is used in soda founts to produce the "foam" on soft drinks, is said to be injurious to the red corpuscles. Many soft drinks purposing to be substitutes for beer and whiskey contain the habit-forming drug *caffein,* which in excessive quantities raises blood-pressure, and which may tend to bring on the degenerative diseases which are responsible for our increasing death rate after middle life.

Coffee substitutes are becoming more widely used, as educated people are beginning to understand the physiological effects of caffein, which is responsible for the coffee habit. Most of them contain chicory, which is probably harmless. The Germans used parched acorns and parched barley as substitutes for coffee. It is probable that all of the coffee substitutes, since they are generally free from caffein, are less harmful than the infusion from genuine coffee beans containing this drug.

German Literature on Food-poisoning.—In looking over the literature on food-poisoning one cannot fail to be impressed by the enormous number of researches on this subject which have been made by the Germans and the great volume of their writings on all phases of the question. In all fairness, we must admit that the Germans should be credited with having made many valuable scientific contributions to the study of food-poisoning, which have advanced our knowledge tremendously regarding the bacteriology and the toxic effects of various food poisons. In studying the German literature on food-poisoning, one is also impressed by the amount of pseudo-scientific mélange that fills their medical books and journals. Perhaps one of the reasons for the German interest in food-poisoning before the war was that they were the greatest gourmands in the world, and ate more raw meats, raw sausage, raw ham, raw dried beef, raw salted fish, and other uncooked meats than any other people. Hence they suffered more from food-poisoning than the inhabitants of any other country.

Conditions are very different in Germany since the war. The people have not more than one-third of the food they had before the war, and the food ration on which they were living in February, 1918, was less than 2,000 calories per adult person. To-day, Germany is a land of starvation. It has always been the land of substitution, and many food substitutes have been placed on the market during their starvation days. Now that the blockade is raised and we shall again have access to German literature, we may expect many interesting contributions on food-poisoning and food deficiency diseases. We can never again have complete confidence in the scientific investigations of the Germans; but it is likely that in their dire need for food during the last two years of the war, they will make contributions of value regarding diet and nutrition. In the future, however, any statement that is made by a German must be verified by other observers before it can be accepted as a fact.

Food Idiosyncrasies.—The old adage that "one man's meat is another man's poison," relates to food idiosyncrasies. *Meat*, particularly veal, oysters, fish, and other proteins, are ordinarily wholesome foods, yet some one of these may be a violent poison to the individual who has an idiosyncrasy for that particular article of diet. The writer recalls a medical society dinner at which the most delicious oysters were served. One of the physicians present (the only one affected) became violently ill a few hours afterwards, suffering from nausea, vomiting and an erythematous rash extending from the tips of his fingers to the elbows of both arms. The attack lasted for less than twenty-four hours. This physician had had similar symptoms several times before from eating what appeared to be perfectly fresh oysters.

Milk and eggs are two of the most important articles of diet for human beings, yet it occasionally happens that a person is found who becomes violently ill from taking one or the other. Symptoms appear similar to those of anaphylaxis, and to those which have been noted in rare cases following the use of therapeutic sera in persons who have been sensitized by previous doses. Undoubtedly the cause of this idiosyncrasy for milk, eggs and other foods containing protein, is a sensitization to proteins which the individual may acquire in some unknown way.

In some instances a food idiosyncrasy seems to be inherited, but in others it is a temporary condition. Individuals may display an intolerance to certain articles of food at one time, and subsequently be able to eat the same things with impunity. The idiosyncrasy to meats, milk, eggs, etc., is called "*protein sensitization*," also "*food allergy.*"

Harper[13] reports a case of food allergy in which an infant suffered from repeated attacks of asthma following the ingestion of even a teaspoonful of cow's milk. He determined to desensitize the infant, and injected two drops of sterilized cow's milk subcutaneously. In five minutes the baby was in convulsions. The skin was cold and clammy, and the infant appeared to be dead. He was revived by a hypodermic of atropin 1/200 grain. The experiment was not repeated.

Protein sensitization may be overcome by giving very small quantities of a food to which an individual has an idiosyncrasy. In case of allergy in infants, where milk is an essential food, desensitization is best obtained by giving very small quantities, beginning with one drop and increasing the quantity daily as the child's toleration increases.

The symptoms from which individuals suffer who have idiosyncrasies for various articles of food vary with the kind of food and with the individual. Protein-containing foods of various kinds, particularly veal and eggs, when eaten by some individuals, will cause violent headache, nausea, and vomiting, and usually constipation, though diarrhea is sometimes observed. A number of well-known clinicians believe that protein putrefaction in the intestines is the cause of many of the manifestations of hysteria and neurasthenia, which are relieved by placing the patient on a low protein diet. Bryant[14] thinks that persons of the habitus enteropticus type, whom he calls "chronic intestinal invalids," are particularly susceptible to the toxic action of the products of putrefaction of proteins in the intestinal tract.

Oysters, crabs, muscles, clams, and other *shellfish* cause nausea and vomiting in some individuals, with abdominal pains and constipation or diarrhea, and particularly a rash, either urticaria, or erythema. Many persons go through life with an idiosyncrasy to shellfish. Others, by taking small quantities, gradually overcome their sensitization to the food for which they had the idiosyncrasy.

Milk, which is an important article of food to most people, disagrees with many, and with some it causes violent symptoms of an anaphylaxis, i.e., dyspnea, prostration, etc. Other persons have an idiosyncrasy for milk, manifested by furred tongue, and slight or even violent headaches. In others, apparently pure milk causes cramps and diarrhea.

With many persons *strawberries* and other acid berries and fruits cause mild toxic symptoms, such as pyrosis due to gastric hyperacidity, nausea, vomiting, diarrhea, and urticaria, the latter being the most constant symptom of the idiosyncrasy.

Acid wines may cause urticaria and diarrhea in persons who are not accustomed to their use. A number of such cases were reported among American soldiers in France who attempted to take up the French custom of drinking light wines.

If one individual out of a group of people, all of whom eat the same food, shows indications of food-poisoning, especially if he is not accustomed to taking that particular article of food, and develops toxic symptoms, he should be warned that he may have an idiosyncrasy for it, and that in future he should partake of only small quantities until he is sure that the idiosyncrasy is not permanent. Care should be taken, however, not to suggest to a patient that any ordinary article of diet is toxic to him, unless there are very strong grounds for the assumption. It often happens that a person becomes ill from infected food, particularly milk, and that he receives the mistaken impression that he has a food idiosyncrasy.

It is undoubtedly true that many people think they have an idiosyncrasy for food when in reality they have not. The author has had many patients who said that they could not take certain articles of food, particularly milk and eggs. On being questioned they gave no history of symptoms due to protein sensitization, and they were induced to take the food that they needed. They had a food prejudice and not a real idiosyncrasy.

It is well, in cases of supposed food idiosyncrasy, to begin with a small quantity of the food which is said to disagree, in order to demonstrate to the patient that he can eat the things which have disagreed with him one or more times before. Whenever a patient has a history of repeated asthmatic attacks, or other severe symptoms in which there is food sensitization after the ingestion of a certain food, it is best not to insist upon the patient taking any quantity of it until his tolerance for that particular food is determined.

The treatment of cases in which the symptoms are thought to be due to food idiosyncrasy, food sensitization, or food allergy, is much the same as that for cases of food-poisoning.

Symptomatology.—The symptoms of food-poisoning vary very much, according to the susceptibility of the affected persons, the type of infection, and the dose received, *i.e.*, the number of pathogenic microorganisms and the amount of the toxins ingested. In an outbreak following a meal at which a number of persons partake of the same food, some may not be affected at all, others may have mild symptoms, while a number may be seriously, or even fatally poisoned.

The degree of susceptibility to food-poisoning depends to some extent upon the age and physical condition of the person affected. Milk that is extremely poisonous to infants may be drunk with impunity by adults, and the person who is debilitated from any cause is more seriously affected than one who is in robust health. Children are more susceptible to food-poisoning than adults. Often it is not possible to estimate the degree of susceptibility of individuals to the toxic effect of contaminated food. Illustrative of this is the case of two boys, brothers, seven and eight years of age, both very strong and robust. Two years ago these boys ate the remnant of ice cream that had been left in the tin freezer for two days; one became violently ill, while the other was not affected. A year later the boy who had not been affected by the poisonous ice cream had an attack of nausea, vomiting, and diarrhea, evidently food-poisoning, while his brother, who had been made ill by eating the ice cream a year before, was not affected, although both had eaten of the same food.

That dosage has an important effect, has been shown in many outbreaks of food-poisoning. Those who eat the largest quantities of infected food are almost invariably the ones who first become ill and have the most serious symptoms.

CLINICAL HISTORY.—*Mode of Onset.*—The onset of food-poisoning is usually from four or five to twelve hours after eating, although in some instances symptoms do not appear for from twenty-four to forty-eight hours, while in a smaller proportion of cases nausea and vomiting occur in a few minutes after the ingestion of the impure food. In the cases in which the toxic symptoms result from the ingestion of formed toxins, the symptoms appear earlier, while in the cases that are true food infections, the manifestations of poisoning do not come on until the bacteria have had time to develop in the stomach and intestines, and there form the toxins. It should also be remembered that both the toxins and the organisms that are ingested may cause toxic symptoms, the first symptoms being due to the toxins generated outside the body. In a few hours the toxic effect from the activity of the pathogenic germs in the body may be manifested.

In the *mild* cases of food-poisoning there may be nausea, vomiting, thirst, abdominal cramps, diarrhea or constipation, headache, dizziness, vertigo; there is little or no fever—often the temperature is subnormal—and only slight acceleration of the pulse-rate. There is tenderness over the epigastrium and sometimes over the whole abdomen. The mild attack usually passes off in twenty-four hours, but in severe cases in which typhoid or paratyphoid bacilli are the infecting organisms, the symptoms may continue for three or four weeks.

In a considerable proportion of the cases in which an individual shows no previous history of digestive disease, and, without apparent reason, becomes nauseated, and perhaps vomits a few hours after eating, the source of trouble is usually some form of food infection. Likewise many cases of diarrhea, without other symptoms, the cause for which cannot be discovered, are due to the ingestion of microörganisms in the food.

The *moderately severe* cases of food-poisoning are characterized by extreme thirst, nausea and vomiting, abdominal pain and tenderness, frequent, and sometimes dysenteric stools, prostration, and a pulse-rate of 100 to 120. The temperature is subnormal in the beginning of the attack, but in six or eight hours rises to from 101° to 103° F. (38.3° to 39.4° C.); this high temperature usually lasts for two or three days, although a considerable proportion of cases are prolonged into attacks closely resembling atypical attacks of typhoid fever.

The *severe* cases of food-poisoning present much the same symptoms as shock from an injury, plus those of gastro-enteritis. Indeed, the patient is in a true state of shock from toxemia. There are the symptoms of collapse, *i.e.*, prostration, the hippocratic expression, rapid pulse, low blood-pressure, cold and clammy skin. There is continuous vomiting. First the contents of the stomach are ejected; then the vomitus may be blood-stained, due to the rupture of veins in the congested mucosa of the stomach from violent retching; later the vomitus contains bile-stained succus entericus. The diarrhea is severe and accompanied by much tenesmus; the stools are often of the choleraic type, or bloody, of a dysenteric character. Rarely, in the severe cases, there may be constipation. The pulse ranges from 120 to 160. The temperature may be subnormal in the fatal, severely toxemic type, and remain subnormal until the end. Ordinarily, however, the temperature rises in a few hours to from 103° to 105° F. (39.4° to 40.6° C.). There may be dizziness and vertigo, sometimes delirium, or stupor, which in the fatal cases deepens into death.

When recovery occurs in the severe cases the symptoms usually subside in three or four days, but the patient is left very weak and debilitated, and convalescence is slow. In a considerable proportion of cases a gastro-enteritis is left, which tends to run a course of several weeks, and may become chronic. In many cases of typhoid fever infection the onset is like food-poisoning, and some cases are so diagnosed; later the gastric disturbance subsides, and the symptoms assume those of a severe and sometimes prolonged attack of typhoid fever.

The nervous symptoms vary very greatly. Ordinarily there is extreme restlessness, and in children convulsions are common. Convulsions sometimes occur in adults, but not frequently. Headaches, insomnia, and marked mental depression, with a feeling of great anxiety, or fear of impending death, are often seen. Muscular and abdominal cramping are often distressing. Delirium may occur in the severe toxemic types, particularly when associated with high fever. Paralytic symptoms have been observed.

In a considerable proportion of cases of food-poisoning, particularly after eating contaminated fish and oysters, there are skin symptoms. Urticaria is the most common skin manifestation. It may last for a few hours, or for several days, and be followed by exfoliation of patches of the epidermis. In some cases there is a diffuse erythema, covering almost the entire body, or involving only the hands and forearms. In this case it is usually bilateral. Many are of the opinion that some cases of eczema and furunculosis may originate from toxins absorbed through the digestive tract. Eczema, particularly, is held to be in some cases a symptom of food allergy, and a number of cases of this troublesome condition have been noted in which the skin test for protein sensitization was positive to meat, fish, eggs, milk, or other foods containing protein. When the use of these foods was discontinued by the patient there was relief from all of the skin manifestations.

The symptoms peculiar to fish- and mushroom-poisoning (pp. 93, 103), and to botulism (p. 101), have been described in the discussion on these conditions.

Diagnosis.—In cases in which several people, who are known to have eaten the same food, develop similar symptoms referable to the gastro-intestinal tract, about the same time after eating, it is safe to make the diagnosis of food-poisoning. It is very difficult, however, to make a positive diagnosis where one person only is attacked by symptoms of poisoning, when others have eaten the same food and not been affected. In such cases it is best not to commit one's self to the diagnosis of food-poisoning until one can exclude the intra-abdominal and intrathoracic lesions in which an acute exacerbation, or complications, may bring on symptoms referable to the gastro-intestinal tract. This is particularly true of cases in which there is an acute attack of pain in the epigastrium, with nausea, vomiting, and constipation. In cases of food infection of sufficient severity to bring on vomiting, this symptom is usually followed in a few hours by diarrhea. In such cases the previous history of the patient is of considerable importance. The writer believes it to be an unusual occurrence for one person to be fatally poisoned by a certain food while others who partake of it escape; yet such cases do undoubtedly occur.

In every severe case of supposed food-poisoning in an adult, there is the possibility that the symptoms are due either to appendicitis, perforated gastric or duodenal ulcer, gall-stones, or pancreatic disease, in all of which pathological states there may be vomiting, with acute abdominal pain and tenderness. Constipation is usually present in all of these conditions, while diarrhea is the rule in severe attacks of food-poisoning. Diarrhea is, however, not an unusual symptom in acute attacks of appendicitis. In angina pectoris and aortitis the pain is often referred to the epigastrium; the attack may come on after a full meal, and often there is vomiting. Cases of apoplexy have been diagnosed as food-poisoning.

The writer has been called in consultation in a number of cases of so-called "ptomain poisoning," in which one or the other of the above conditions was the real cause of the symptoms. He recalls one tragic case, in which an excellent surgeon had treated the patient medically for several days, because he had attributed his illness to eating soft-shell crabs. An operation five days after the onset of the symptoms revealed a gangrenous appendix, with general peritonitis, from which the patient died. Another case of so-called "ptomain poisoning" was the first attack of angina pectoris which came on with pain, nausea, and vomiting soon after eating. The patient died of a second similar attack. Another case is reported in which the patient was observed several days after a sudden attack of vomiting, with pain in the epigastrium, and only a few hours before death. The autopsy showed perforation of an old gastric ulcer. An instance is recalled in which an operation for a perforating duodenal ulcer was delayed for three or four days, because the patient thought he had "ptomain poisoning," or "acute indigestion."

In the case of the *sudden death* of an adult, supposed to have "ptomain poisoning," or "acute indigestion," in which no other member of a family is affected, the diagnosis is most important, particularly if there is a medicolegal aspect to the case. It is probable that in the majority of such cases, unless there is proof that the patient has partaken of infected food, death is due to one of the diseases of the thoracic or abdominal viscera previously mentioned. It is certain that there will always be a question in the diagnosis in such doubtful cases, unless an autopsy is performed by a skillful physician. In case lesions are found, it is advisable to preserve the specimens.

Pathology.—An autopsy should be performed on every fatal case in which there are symptoms of food-poisoning. There are almost certainly lesions of the gastro-intestinal tract in every case of food-poisoning in which there is severe vomiting and diarrhea. Most of the autopsies which have been reported have shown acute inflammatory lesions of the stomach and intestines. There is usually redness, and swelling of the mucosa, which is covered with thick, tenacious mucus. In the severe cases there is necrosis with sloughing, leaving ulcerous patches in various parts of the gastro-intestinal tract. Microscopical examination shows degenerative changes, *i.e.*, cloudy swelling with exfoliation of the epithelia of the mucosa and the glandular structures. The blood-vessels are dilated and there may be punctate hemorrhages in the walls of the stomach and intestines. There is also the usual round-cell infiltration of inflammation.

BACTERIOLOGICAL EXAMINATIONS IN SUSPECTED CASES OF FOOD-POISONING.—It is important, in every case in which the illness is thought to be due to food-poisoning, that the food which is left over, or that which has been vomited, and the stools of the patients, should be thoroughly examined. The methods adopted by the Food Division in the Surgeon General's Office of the United States Army might well be employed in civil life. If the physician in charge of cases of suspected food-poisoning is not prepared to make thorough bacteriological examinations of food, specimens should be placed on ice and sent as promptly as possible to laboratories which have the facilities for such investigation. There is much to be learned about food infection, and the coöperation of the general practitioner with bacteriologists and food experts is needed to clear up many matters not yet explained.

The following instructions for cases of suspected food-poisoning were sent to various base hospitals in the United States Army by the Food Division of the Surgeon General's Office:

1. Food-poisoning is probably most generally produced through the agency of specific microörganisms of the Gärtner's bacillus group, sometimes by *Bacillus botulinus,* and possibly sometimes as a result of putrefactive changes due to *Bacillus proteus* and closely related species.
2. In cases of food-poisoning, therefore, search should be made for

organisms of these groups in the suspected foods and in the intestinal tract or discharges of those affected, in such numbers and relations as would explain the outbreak. In case of fatalities portions of spleen, liver, bone-marrow, and intestines should be taken, ligatured to retain the contents. Blood-serum from many of the persons attacked should also be collected.

3. All samples must be accurately labeled, all points regarding the sample being noted, such as age, conditions under which it has been kept, whether taken from outside or inside of a large piece, etc.

4. All samples not examined at once should be carefully sealed and kept or sent packed in ice-boxes.

5. *Bacteriological Examination:* A uniform and characteristic sample should be prepared, then:

(*a*) Aërobic and anaërobic cultivations for the separation of the types of organisms should be made.
(*b*) Feeding tests should be made with mice, rats, or guinea pigs, portions of the original sample being used, and also pure cultures obtained therefrom on sound or sterile foods.
(*c*) Subcutaneous and intraperitoneal inoculations should be made from the cultures obtained. If any animals die, postmortems should be made. A check must be kept on all tests.

6. A sample most convenient for use can be made by mincing selected portions of the food or tissue in sterile water, salt solution or broth, using sterile instruments, and then mixing thoroughly. If quantitative results are desired a definitely weighted or measured amount of the sample must be taken.

7. Examination for the *Bacillus coli* group. The general procedure should be as in the water examination, *i.e.*, the use of sugar broths, peptone solution, litmus lactose, agar plate, endo plate and Russell's medium.

8. Examinations for the *Bacillus proteus* group. Five per cent. gelatin plates should be used, and all proteus-like colonies examined, whether liquefying or not. Reactions should be tested in sugars, Russell's medium, peptone solution, and on blood serum, casein and gelatin.

9. Examination for *Bacillus botulinus.* This organism is a large anaërobic bacillus with terminal spores resembling *Bacillus tetani.* The spores have not great resistance to heat, being destroyed by boiling. Samples of food should be examined microscopically for the appearance of this organism, and also by making anaërobic cultures in gelatin, dextrose, lactose and saccharose broths, and in milk. The organism produces a rancid butyric acid odor, and powerful toxins (saprophytically) which produce paralysis or death when inoculated into rats or other rodents. The organism is harmless when ingested, as it will not grow in the body. The danger is from its action on protein (especially

sausage, etc.) before the food is eaten, rather than from direct infection.

10. Examination for Gärtner's bacillus group. Plates of lactose, salicin, saccharose, neutral red bile-salt, agar (Savage) should be prepared, and the surface brushed or smeared with the emulsion supposed to contain the organism. The white colonies which develop should be examined by subcultivation in fermentation tubes containing litmus and salicin, saccharose and lactose broths. Tubes showing no acid or gas after two days at 37° C. (98.6° F.) should be examined, both culturally and by inoculation and agglutination tests. Inoculation of the original emulsion into dulcite malachite green broth is advisable, as an enrichment process followed by the treatment of the plates is indicated. The agglutination tests will be necessary to separate the two strains, *Bacillus enteritidis* and *Bacillus suipestifer* (*choleræ suis*).

Treatment.—PROPHYLAXIS.—Food-poisoning is really a question of public health, and it should be the duty of physicians to report cases to the health authorities for investigation, to find, if possible, the source of food contamination, in order to prevent others from becoming infected. For instance, if it has been definitely proved that one person is poisoned by taking food which is sold on the market, and used in the home, the remainder of the product from the same source should be investigated before it may be sold or used by others.

SYMPTOMATIC TREATMENT.—The most important indication for treatment in any case of suspected food-poisoning is to **empty the stomach** as quickly as possible, particularly if the patient has not vomited thoroughly. **Lavage** with warm water is the best method, and it should be kept up until all the contents of the stomach have been removed. A large-sized soft rubber stomach-tube with openings sufficiently large to let food pass through should be used. Some authors advise **boric acid**, one tablespoonful to a gallon of water, on account of its antiseptic effect. The writer prefers a **solution of sodium bicarbonate**, one ounce to one gallon of water. There is gastric hypersecretion early in food-poisoning, and later the symptoms of general acidosis may occur; if some of the alkaline solution is retained it will probably be helpful.

In cases in which there is considerable retching so that a tube cannot be retained in the stomach, two or three gobletsful of **luke warm water** in which there are one or two teaspoonfuls of sodium bicarbonate, or the same amount of **sodium chlorid**, followed immediately by vomiting, will aid in clearing the stomach. The best apparatus for washing out the stomach of children is a large-sized catheter, attached to rubber tubing, with a funnel at one end.

In the event that a stomach-tube is not available, **apomorphin hydrochlorid**, 1/10 grain (0.0065 gram) every half hour, may be given hypodermatically until vomiting results. It is advisable when vomiting is brought on by apomorphia to have the patient drink several goblets of tepid water in order to thoroughly clear the stomach of toxic material. Vomiting may also be induced by **inserting the finger down the throat** and tickling the fauces. **Emetics** like mustard, tartar emetic, and ipecac, classed as irritants, should not be used when gastric lavage is practicable; but if the stomach cannot be emptied in any other way their use is permissible. **Ipecac** is probably the least irritating and it may be given to adults in the powdered form, 5 to 10 grains (0.324 to 0.65 gram) in water every ten minutes, until vomiting is brought on. The syrup of ipecac is probably the best form for children, one-half teaspoonful every ten minutes, to a child of five years, until vomiting is induced.

The **bowels** should be thoroughly **evacuated** as soon as possible. Even if they have moved well and there is diarrhea, **enemata** should be given, large quantities of water being advisable. If there is no free bowel movement after the stomach is cleared out, a quickly acting purgative such as **magnesium sulphate,** ½ ounce (15.55 c.c.), or **castor oil,** 1 ounce (30 c.c.), should be given.

Small doses of **calomel,** grain 1/10 (0.0065 gram), every hour for five doses will often relieve nausea and will have an "antiseptic" effect on the intestines. The probable effect of the calomel is to cause the gall-bladder to empty its contents into the intestines. Bile is said to inhibit bacterial development, which no doubt accounts for the so-called "antiseptic" effect of calomel. The writer wishes to take this occasion to protest against the large doses of calomel, 5, 10, or 20 grains (0.324, 0.65 or 1.3 grams), given by some physicians. A maximum dose of from ½ to 1 grain (0.0324 to 0.065 gram) will have just as good an effect without producing the depressing effect of large doses of mercury; also with the small dose there is little, or no, danger of salivation. If the bowels have not moved well within four or five hours after the administration of calomel, in food-poisoning or in any other condition, it is best to give a laxative of some kind, such as **magnesium oxid,** grains 20 (1.3 grams), repeated every three hours until there is free catharsis.

In many cases after the stomach has been thoroughly emptied the nausea will subside, but if it persists, the application of an **ice-bag** to the epigastrium is helpful. If there is pain with griping, the **hot-water bottle, hot packs,** the **electric pad,** or other hot applications to the abdomen, may add to the comfort of the patient; but unless there is pain, the ice-bag is preferable.

In cases of food-poisoning where there is nausea, vomiting, cramps, and diarrhea, there is the greatest temptation to give a hypodermic of morphin, the "abdominal splint" of the older writers, to relieve the immediate symptoms. It will give patients temporary relief and allow the doctor to go to other patients, or to obtain some very much needed rest; but **morphin, codein,** or any other form of opium should **never** be **given** in food-poisoning **until the stomach and intestines have been thoroughly emptied.** It is true that the patient may be very wretched, and suffering intensely; but his sufferings may be better borne if it is explained to him that nausea, vomiting, and diarrhea are simply Nature's efforts to throw off the poison, and that any medicine strong enough to stop these symptoms will "lock up" in the stomach and intestines poisons, whether bacterial or chemical, that should be removed from the gastro-intestinal tract. However, after the stomach and intestines have been cleared out, if there is still intense pain, severe retching, or very frequent stools accompanied by great pain, the morphin may be admissible. In most cases morphin, codein, or any other form of opium is not only unnecessary, but harmful.

If there is nausea or vomiting, **oxalate of cerium**, 5 grains (0.324 gram); **bismuth subnitrate**, 10 to 15 grains (0.65 to 0.972 gram); **menthol**, 2 grains (0.13 gram); **carbolic acid**, 1 minim are indicated; one or the other, or two of them in combination in mint water, every one or two hours, may have some effect as a gastric sedative. When there is burning in the stomach, sodium bicarbonate, dram i (4 grams), in mint water, drams iv (15.5 c.c.), every two hours, may be helpful.

After the acute symptoms have subsided, a prescription which Dr. Charles G. Stockton, of Buffalo, calls "gastric sedative" is very helpful when an antacid and mild laxative are desired. The prescription is as follows:

Cerii oxalatis	ʒ ii	(8 grams)
Bismuthi subcarbonatis levis	ʒ iv	(16 grams)
Magnesii carbonatis U.S.P.	℥ i	(32 grams)

Sig.: ½ to 1 teaspoonful stirred in ⅓ goblet of water every 3 to 4 hours.

If there is diarrhea, **bismuth subnitrate** in large doses, 1 or 2 drams (4 or 8 grams) every two hours, if the bowels act that often, is a good astringent, and it apparently has some effect in inhibiting bacterial development in the intestines. **Salol** in 5 grain (0.324 gram) doses given with the bismuth seems helpful, and **resorcinol**, grains ii (0.13 gram), is also a good intestinal antiseptic.

After one or two days the gastric hypersecretion in food-poisoning subsides and then there is usually subacidity as in any form of subacute gastritis. **Dilute hydrochloric acid**, in doses of 15 minims (0.92 c.c.), thoroughly diluted, may be given immediately after the ingestion of food, after the first two or three days, and may be continued until all symptoms have subsided. The hydrochloric acid is not only helpful in stomach digestion, in subacidity, but is also of value in controlling the putrefactive diarrhea which sometimes continues for several days in food-poisoning after the nausea and vomiting have subsided.

In the severe cases in which the patient is in a state of shock from profound toxemia—with low blood-pressure, rapid pulse, subnormal temperature, leaky, cold skin, great restlessness, and anxiety—the same treatment is indicated as for traumatic shock. It is important to maintain, or to restore, body temperature; the patient should be **kept warm** by the application of hot-water bottles to the extremities, and by being well wrapped in blankets.

There is nothing better for shock, after operation, than the use of heat applied within the stomach by the use of hot water in gastric lavage. In the shock of food-poisoning, there is even greater indication for gastric lavage, because it not only applies the heat within the body, but removes the bacteria and the toxins which cause the trouble. The use of **hot colonic irrigations** are helpful for the same reason. If the patient is retching to such an extent that a stomach-tube cannot be retained, **hot drinks**, coffee, tea, or plain hot water, with or without the addition of soda or salt, is helpful. If vomiting continues after the hot drinks the patient is all the better off, because in vomiting the water, coffee or tea, he eliminates some of the toxins or bacteria. If the tea or coffee is retained, the caffein which they contain is one of the best stimulants that can be used in shock of any kind.

The use of **stimulants hypodermatically** is also indicated. **Caffein citrate,** grains ii (0.13 gram) or **camphor,** grains iii (0.195 gram) in sterilized oil, minims xv (0.92 c.c.), are the best stimulants, next to transfusion. What Cannon[15] calls "the critical level of a falling blood-pressure" applies to the severe cases of toxemia from food-poisoning, as well as to the shock from an injury or from hemorrhage. It would seem that the transfusion of blood, or the intravenous use of the normal salt solution, is indicated more in the treatment of shock from acute toxemia than in trauma or hemorrhage. In the shock of toxemia, transfusion not only adds volume and vital elements to the blood stream, but also decreases toxemia by diluting the toxin circulating in the blood. Alcohol in any form is contra-indicated in food-poisoning for the reason that it is an irritant to the stomach and, since it lowers blood-pressure, it is not a true stimulant.

While there are many reasons for withholding morphin, or other forms of opium, in most cases of food-poisoning, yet in patients who are in a state of shock, with extreme restlessness, great anxiety, depression, and excessive pain, nausea, and vomiting, **morphin** is indicated. But the efforts to eliminate the poison by lavage, colonic irrigations, or by purgatives should be continued, because there is all the greater need for it after the use of a drug that "locks up the secretions," and which, by its action on the musculature of the stomach and intestines, interferes with Nature's efforts to eliminate bacteria and toxins, or the chemical irritants which are responsible for the damage to the tissues of the body in food-poisoning.

DIET.—Diet is more important than medicines in the treatment of food-poisoning. It is best to give no food of any kind for from twenty-four to forty-eight hours, depending upon the severity of the symptoms at the time when food is given.

Cracked ice may allay gastric irritability and may be used freely. Because of the vomiting and diarrhea in food-poisoning, the tissues of the body are partially dehydrated, and the thirst which is usually present is Nature's call for water. If the stomach will tolerate it **water** may be given freely by mouth. If not, it should be given in large quantities per rectum by the Murphy drop method. If there is great irritability of the rectum, with frequent stools, fluids should be given subcutaneously or intravenously in the severe choleraic type.

It should be remembered that in food-poisoning digestive function is so disturbed that but little, if any, food will be disgested for two or three days after this gastric and intestinal trauma has occurred. The processes of digestion are seriously impaired, and instead of being assimilated as nourishment, certain foods "add fuel to the fire," because in this condition the stomach and intestines generally contain myriads of microörganisms, which grow best on culture mediums, like milk, meat broths, and other foods in which protein is an important factor.

Bland sterilized carbohydrates are indicated for the first two or three days after food-poisoning. **Barley water** allays thirst and furnishes as much food as the patient can digest for the first day or two. Barley water is easily prepared by mixing one teaspoonful of Robinson's patent barley flour to one pint of water, and boiling for 15 minutes. A pinch of salt, or lemon or orange juice and milk sugar, or a little cane sugar, may be added to the barley water. It may be given hot, or very cold with the addition of cracked ice. Toast water (boiling water poured over dry toast) to which a little butter and a pinch of salt may be added, is palatable to some. Mellin's food (a tablespoonful to 1 pint of boiling water) is a good soluble carbohydrate.

When the nausea and vomiting have subsided, barley gruel, strained oatmeal gruel, or corn meal gruel may be given. The first solid food to be given may be dry toast or toasted crackers and butter, rice and butter, or strained oatmeal. Orange or lemon sherbet, or other ices of which milk is not an ingredient, may be given as soon as the stomach will tolerate water. Indeed, the ices may allay nausea.

The return to solid food, and to the regular diet, should be gradual. The appetite is not always a good guide as to the need for nourishment in food-poisoning. The subacutely inflamed stomach may often produce a sensation of epigastric discomfort, which may be mistaken for hunger, and which may be aggravated by giving food. If the physician errs in dieting a patient who is convalescent from an attack of food-poisoning, it is apt to be in the direction of giving too much food, and in allowing the patient to return to his regular diet before the digestive functions have been fully restored.

REFERENCES

1. JORDAN, E. O. Food-poisoning. Univ. of Chicago Press, 1917, p. 77.
2. GUDGER. Weeding out the poisonous fishes. Scient. Amer., Jan., 1919, lxxxvi, 28.
3. CLARK, A. H. Shark intoxication. Science, New York and Lancaster, Pa., 1915, xli, 795-797.
4. JOHNSON, G. A. Shellfish conservation and sewage disposal. Am. Jour. Pub. Health, New York, 1914, iv, 965-968.
5. GORHAM, F. P. Seasonal variation in the bacterial content of oysters. *Ibid.*, 1912, ii, 24-27.
6. CHESTNUT. U. S. Dept. of Agricult., Div. of Botany, 1896, Bull. 20.

7. Harris and Cockburn. Alleged potato-poisoning. Am. Jour. Pharm., Oct., 1918, xc, 722.
8. Wynn, W. H. Food-poisoning. Clin. Jour., London, August, 1918, xcvii, 122.
9. Jordan, E. O. Food-poisoning. Univ. of Chicago Press, 1917.
10. Wiley. Foods and their adulteration. P. Blakiston, Philadelphia, 1917, p. 314.
11. U. S. Dept. of Agriculture, 1911, Report 94.
12. Jordan, E. O. Food-poisoning, 1917, p. 16.
13. Harper, W. W. Tr. Med. Assn., Alabama, 1917, xxxiv, 484.
14. Bryant, John. Getting results with the chronic intestinal invalid. Tr. Am. Gastro-enterol. Assn., 1918, xxxi, 203-209.
15. Cannon. Traumatic shock and hemorrhage. War Med., Dec., 1918, ii, 770-789.

CHAPTER VII

MILK-SICKNESS

By Arthur J. Clay, M.D.

Definition, p. 123—Etiology, p. 123:—Predisposing factors, p. 123; Exciting cause, p. 125:—The plant, p. 125; Pasture and live stock, p. 126—Symptomatology, p. 126:—Intoxication, p. 126; Symptoms and signs in animals, p. 126:—Cattle, p. 126; Horses, p. 127; Mules, p. 127; Sheep, p. 128; Buzzards, p. 128; Dogs, p. 128; Hogs, p. 128; Immunity, p. 128; Postmortem, p. 128—Symptoms and physical signs in man, p. 128:—Acute form, p. 128; Sub-acute or chronic form, p. 129—Diagnosis, p. 129:—Differential, p. 129; Clinical p. 129; Laboratory, p. 129—Treatment, p. 130:—Prophylaxis, p. 130; Medicinal treatment, p. 130—Prognosis, p. 130—Pathology, p. 130.

Definition.—This disorder has been known under many names, suggested by common symptoms or by some theory as to its etiology, yet owing to the fact that a high percentage of the cases are due to the use of milk, no better term can be applied than "milk-sickness." In live stock the predominant symptom is trembling, and therefore "trembles" may be a better name.

Many writers have tried to limit geographically the area chiefly affected, such limitations failing because of the fact that so little was known of the origin of the disease. The writers or investigators forgot to note the environment of the outbreak, and failed to see its relation to the thickly-wooded pastures and to the virgin soil in its primitive state, with its wild vegetation.

Very little is known of the disease, due to the fact that about the time that scientists began to study it, it ceased to exist, because the clearing and the cultivation of the land had caused its almost complete extermination. Yet as long as North America has uncultivated land with climatic conditions favorable to the growth of a certain plant to be described later, milk-sickness will exist. Consequently it is still of interest to the medical profession, for at any time a physician may come in contact with a case appearing far removed from the seat of its origin, or at a season when the plant is unobtainable, the sickness having been carried by dried beef, butter, or cheese.

Etiology.—Predisposing Factors.—Judging from results of personal experiments, much clinical study, and a preponderance of evidence obtained from other investigators, the author believes that this disease is an *intoxication,* rather than an infection, as is believed by some, who, however, have thus far failed to demonstrate a specific bacillus. Those who have advocated the mineral theory have also failed to prove their case. *Water* cannot be considered as a factor, although some writers mention as a causative factor a dry season following an overflow or wet season. Others speak of marshy places, sloughs, etc., as contributory causes, but this theory will not hold. The author has visited many pastures containing the plant, that had neither a stream nor marshy places, and that were too high for an overflow, the stock drinking well-water. Yet the cattle were victims of trembles. Then, too, other stock drinking the same water, but feeding in another field, showed no signs of illness.

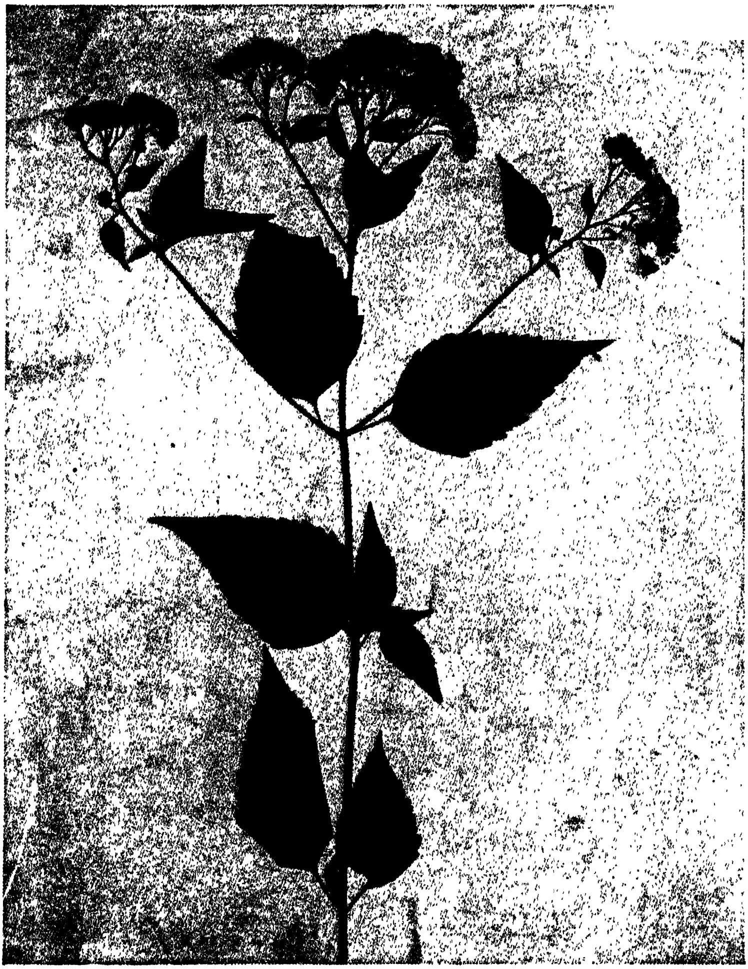


FIG. 1.—EUPATORIUM AGERATOIDES.

In one family of seven persons, five were sick. All drank the same water, but the two who escaped used no milk or butter, while the five who succumbed did. One of them died. The suckling calf of one of the milk cows which supplied this family also died.

Herbivorous animals are first affected, especially the cow. Carnivorous animals then develop the malady when fed on the diseased carcasses. The disease is, in a way, self-propagating, and the author has noticed that under some conditions it passed on from one animal to another which had fed on the *milk* or *meat* of its predecessor. This may be due to the fact that the latter had received a maximum dose of the intoxicant, and that the tissues were completely or nearly saturated with it, transmitting it to the animals which ate the meat. These in turn spread the disease further.

Season.—In the beginning of August of the extremely dry years, and up to the latter part of October, cases are most numerous. At this time *Eupatorium ageratoides* thrives best. The dry season seems to affect its growth kindly. It grows only in the shade. Many cases of the disease have been reported out of season when the plant was not growing and trembles was not found among the live stock. These can be accounted for by the use of cheese, cured or dried beef, and honey from bee trees.

EXCITING CAUSE.—Under this head the author will discuss the disease in man as an intoxication from the alkaloid or active principle of *Eupatorium ageratoides,* which is transferred to man through the medium of milk, butter, cheese, beef, and pork. The order in which these articles are given corresponds approximately to the relative frequency with which they transfer disease.

The Plant.—The *Eupatorium ageratoides* (the white samicle) is usually found in the rich soil of a thickly-shaded oak ridge near a small stream with a sandy bottom. The more shade there is, the thicker it grows, its season being from July to November, inclusively. It blooms in September, and has a white blossom of the corymb type, consisting of a cluster of flowers, each on its own foot stalk and arising from a common axis, and each having a fringy bloom. The stalk is from one to four feet high, with a square stem, and has opposite petioled leaves broadly oval at the base, taper-pointed, coarsely toothed, three-ribbed and veined, thin and easily skeletonized by insects that feed on the leaves of this species of plant. The leaves grow in pairs from alternate sides of a stalk, so that each pair is at right angles to the pair above or below it. Just before and during the time of bloom, the honey-bee and other small bees, wasps, etc., cut many holes in the leaves, using the parts for honey-comb. The blue butterflies frequent the bloom, gather nectar, and transfer the pollen. The roots are many, and all of about the same size, varying from four to twelve inches in length. They are pearly white, spread out, and grow only about three inches deep. They wilt and turn brown almost immediately after having been pulled, and then become wiry. The plant thrives well in dry weather, the leaves and stem remaining green when neighboring plants are parched. If cut, the stems may be kept growing in a basin for about six to eight weeks, although there are no roots on the stems. The parts in the water turn black.

Pasture and Live Stock.—A discussion of this topic is necessary in a study of the etiology of the disease. During the dry seasons, when all the grass is gone, when the heat is intense and flies are numerous, the herbivorous animals are driven to the thickly-wooded pastures and shaded places to knock off the flies against the thick brush and weeds. Rather than venture out again into the open, they browse among the green and juicy wild plants, and if the *Eupatorium ageratoides* is present, one finds that it is more bitten than any other foliage. The author noted this fact after the loss of many cattle, sheep and horses. Consequently he procured three head of healthy stock (two young cattle and one sheep) which had not been in wild pasture, fenced them in a barren lot, and compelled them to eat the plant, cut fresh at each feeding. Within three days all were dead, the symptoms and signs being identical with those of the cattle which had died previously.

Symptomatology.—INTOXICATION.—The intoxication period usually lasts from two to five days, and the poison, judging from its physiological action, seems to have cumulative properties at first, and then to suddenly begin to act acutely. In many cases no premonitory symptoms are noted, except a few hours of weakness.

SYMPTOMS AND SIGNS IN ANIMALS.—This subject will not be taken up in detail, but, because of the similarity of the symptoms to those of the disease in man, it is necessary to give a summary of the predominant symptoms and physical signs which are noted in cattle, horses, mules, sheep, dogs, buzzards and hogs. The greatest emphasis will be placed upon the cattle, as they often transmit the disease to human beings through their meat or milk.

Cattle.—The first symptoms of the disease observed are listlessness and indifference to food. The animal will try to drink, but is disinclined to move about, holds its head low, and watches the ground closely as it steps (similar to a man with ataxic gait). The eyes have a glaring, protruding appearance. The animal is unable to walk straight and fails to keep pace with its fellows, stops to rest, attempts to evacuate the bowels, the muscles on the shoulder quiver, and the front legs seem weak, while the hind legs are stiff. It is unable to walk across uneven ground; it falls, lies panting, and is unable to rise. If tame it will allow itself to be helped up, but if wild it will fight, and will die of exhaustion. These first characteristic signs give place to the more severe symptoms of the second stage, characterized by great weakness and clonic contractions. If the animal is able to get up, the front legs seem too weak to hold its weight, and the extensor muscles are paralyzed, causing the flexed position, which continues until death occurs. The hind legs remain extended, although many clonic contractions of the muscles are noted. The neck is usually twisted to one side, some of the muscles being hard and stiff. Later in this stage the head is extended, the eyes are red and protrude upward, and there is a gummy, yellow discharge. The breath has an acetone odor in all cases. Sometimes, if the animal is wild, or if it is disturbed, it may have a thin, muco-bloody passage from the bowels, with an odor similar to that of the breath. The majority die without having had an evacuation of the bowels. The milk cow is less likely to die, as she seems to eliminate the toxic product through the milk, yet she may have all the first signs noted in steers, and if caused to go dry she will die also. The milk of the affected cow is not unusual either in odor or taste. The milk cow may be driven considerably more than other animals and show scarcely any signs of exertion, yet her milk may be very toxic, and may cause the death of persons using it, long before she is suspected of being the contributing cause. After severe exercise, however, she will be found on close observation to give out the same fetid odor as the other animals. (The hog gives forth no odor, this fact being attributed to its lack of sweat glands.) The pulse is very irregular, the temperature is always from 1°-2° F. (.55°-1.10° C.) lower than normal; the gastro-intestinal tract is distended with gas; a slight groaning, and the Cheyne-Stokes rhythm of breathing are heard. During this stage signs of pain are manifested, and a continuous movement of one of the front legs is noted while the animal is in a semiconscious condition. Finally, in the last five or six hours, all consciousness is lost, and death seems painless.

Horses.—In the case of a colt, which died after symptoms similar to those described above for cattle, the mother's milk caused the sickness, yet she did not manifest any symptoms of sickness until hitched to a load (about the time that her milk was failing). She then stopped, failed to respond to the whip, fell, and never got up, dying in nine hours. Before she fell she trembled all over, and after falling had clonic muscular contractions of the front legs, digging grooves in the ground with her hoofs. She held her head to one side; at times she groaned, then she would stretch herself out flat and strike out with both front feet. These symptoms finally abated, and she was apparently unconscious until death. The eyes, respiration, odor, and temperature were similar to those described above for cattle. Other horses that died were affected similarly to steers, the symptoms beginning with a slow drooping and weaving gait, which, as the disease progressed, gave way to a tendency to fall, and inability to rise. None of those observed lived over seven days.

Mules.—Mules are as a rule not much affected. None of the cases observed died, and only two showed marked signs. One, a nursing mule, was slightly affected at the same time as its mother, but neither died. Both exhibited the symptoms of the first stage. The other mule showed marked symptoms of trembles when hitched to a plow, but, after a few days' rest, it seemed to recover. Its predominant symptoms were: slow movements, droopiness, trembling, and failure to eat. The author has heard of, and seen, quite a number of sick mules, but has observed no fatalities, and other writers have mentioned no deaths. The author attributes this partly to the nature of mules in regard to eating. They are more particular about what they eat, and never over-eat. The *Eupatorium ageratoides,* when bitten or crushed, gives off a peculiar, disagreeable plant odor that seems to discourage the mule from eating it.

Sheep.—Sheep are guarded against eating this plant by its odor, while horses and cattle seem to pay little or no attention to plant odors and will eat anything green. Out of a herd of seventy sheep only four died, although many others seemed "off their feed." Those that died displayed symptoms similar to those of the cattle, the predominant symptom being the tendency to lie flat and dig grooves in the ground with their feet.

Buzzards.—Buzzards were observed which had eaten the carcasses of diseased horses and cattle. Some of them died, and some were slow to fly when approached, but the author had no opportunity to study their symptoms.

Dogs.—Dogs which had eaten the flesh from the carcasses of diseased horses died within three days. Vomiting and weakness were their worst symptoms.

Hogs.—One sow that had eaten the flesh of a dead cow did not seem affected, but four of her seven pigs were sick, being bloated, and breathing rapidly when lying stretched out. They were unable to suck or to follow their mother for three or four days, but finally recovered.

Immunity.—No animal is immune, but the herbivorous animals seem more susceptible, and more fatalities are reported among them than in the case of the carnivorous animals. Neither acquire immunity by an attack. Human beings, also, may have repeated attacks, or relapses due to the cumulative properties of the intoxicant.

Postmortem.—The author performed a postmortem on two horses and one cow. All showed a capillary injection of the lining of the gastrointestinal tract, the intestines being loaded with food which the animals had eaten before showing signs of illness. Bloody mucus was also present. Other organs appeared to be normal, except that the liver was congested and enlarged.

SYMPTOMS AND PHYSICAL SIGNS IN MAN.—*Acute Form.*—The first symptoms in man are anorexia, languor and fatigue, later, nausea and vomiting. The patient is unable to take food or water, owing to the pernicious vomiting, which may be continuous, lasting from one to two or three days, when complete exhaustion is followed by restlessness and mental dullness. This stage is succeeded by semi- or complete unconsciousness. Obstinate constipation is found; the urine is scant and pale in color. As the case progresses, the patient complains of pain in the abdomen and at times in the calves of the legs, followed by stiffness. Hiccough and dysphagia are also noted. Extreme thirst is the rule, and the patient's breath has a *fetid odor* which resembles that of acetone or chloroform. This is the *most characteristic diagnostic symptom* of the malady. When the patient is directed to protrude his tongue, a decided tremor is noted. The tongue is red, unusually large, and later becomes sore and parched, with fissures. The pupils react sluggishly, the conjunctivæ are reddened, the eyes are rolled upward in the semiconscious state, and there is a yellow, gummy discharge at each canthus. The abdomen is scaphoid, and later tympanites occurs.

Convulsive seizures are occasionally observed; the patient usually lies on his back, with his head turned sideways, and his legs drawn up with the knees spread far apart. Tendon reflexes are sluggish. The skin is cold and clammy, the pulse irregular, varying from 70 to 120, the temperature subnormal, rarely exceeding 99° F. (37.2° C.); the blood-pressure is about 95 and even falls as low as 67. Respiration is irregular, and of the Cheyne-Stokes type.

Sub-acute or Chronic Form.—The symptoms of this form are about the same as in the acute. Produced by the same cause, they differ only in degree. The patient is languid, vomiting only by spells. At times he seems a little better than at others, yet he is unable to exert body or mind. The appetite for food and water varies; the patient may eat, but eating causes a relapse. There is palpitation of the heart at times, and stiffness of the legs, with cramps in the calf muscles. The liver is enlarged, the skin wrinkled and yellow. Perspiration and breath have the acetone odor. The tongue is swollen, clean and red, and gives no reflexes. Tenderness is observed over the jejunum and ileum, and gas-gurgling is heard in that region. Respiration is irregular. There is marked emaciation. The eyes are half open; the conjunctivæ may be yellow. The patient may vomit blood or pass bloody stools. Blood-pressure may be as low as 70. In one case it was 67; when the blood-pressure reaches such a low level the case is fatal. The writer might mention here that in such cases the blood-pressure is the lowest on record, even reaching from 5 to 7 mm. This is below the figures for typhoid cases, which up to this time have held the lowest record. Low blood-pressure may be explained as due to the dilatation of the gastro-intestinal blood-vessels, and of the central veins of the liver, which thus add their effect to the cutaneous vasodilatation. The temperature is usually subnormal, but may reach 100° F. (37.8° C.), or possibly even higher, just before death, due to some complication. This stage may continue for months, or may be transformed at any time into the acute form by over-exertion or over-eating. In convalescence, weakness and trembling are noted, and if the patient attempts to run, the adductor muscles relax, so that at each step his feet become farther separated, until he falls.

Diagnosis.—DIFFERENTIAL.—The vomiting, in the subacute stage, is similar to pernicious vomiting in pregnancy, but can be easily differentiated by a careful study of the history. Other symptoms are characteristic of this disease alone, and if a careful examination is made, no excuse can be offered for a mistaken diagnosis. Vomiting in pregnancy is often accompanied by acetone and diacetic acid in the urine.

CLINICAL.—The points to be noted in making a diagnosis are: the appearance of the tongue, the odor of the breath, vomiting, and subnormal temperature.

LABORATORY.—These findings should be closely observed, yet the only result gained is the elimination of suspicious etiological conditions. The author has made repeated examinations of milk, both chemical and microscopical, but in no case has he found a trace of the *Bacillus lactimorbi.*

Feces.—The feces give an acetone odor, and an acid reaction.

Urine.—The urine is pale and scant, and gives an acid reaction; the specific gravity is from 1.020 to 1.030, with traces of acetone and albumin. The fact that some cases showed no albumin might be attributed to the free use of sodium chlorid in the treatment. This will diminish the quantity of albumin, as in acute nephritis.

Vomitus.—One finds a mucoid, tenacious material, with an acetone odor, which gives an acid reaction, and later may contain blood.

Blood.—There is no leukocytosis. The white cell-count is from 8,500 to 9,400 about the eighth or ninth day of illness:

Lymphocytes, 11.8 per cent.
Small lymphocytes, 4.95 per cent.
Large lymphocytes, 5.2 per cent.
Polynuclear neutrophils, .87 per cent.

Treatment.—PROPHYLAXIS.—If possible, clear the ground and plow it to destroy the plant, or burn over the woods after the leaves have fallen. Avoid the use of thickly-wooded pastures during the dry seasons. In case of sick cattle avoid the use of milk and, in case any stock is lost, burn the carcasses.

MEDICINAL TREATMENT.—Owing to the fact that the active principle of the plant has a marked affinity for alcohol, nothing is better than the use of **alcohol** as an antidote, up to the degree when its physiological action is noted (intoxication). Avoid purgation. Use **sodium chlorid** and **sodium carbonate** in equal parts, 15 grams to the pint, per rectum, every two hours. In the sub-acute cases **castor oil** may be used, in addition to the above. Among the first foods which may be successfully given are salt-cured meats, with fruit wines.

Prognosis.—The outlook is very grave in both acute and subacute cases. The acute cases usually die between the second and ninth day. If there is any predisposition to tuberculosis, the time is never more favorable for the work of the tubercle bacilli than in the subacute cases. If the patient is not tuberculous, but is sick for many weeks or months, the probability is that he will become permanently demented, or die as a result of the cardiac failure which gradually develops.

Pathology.—Milk-sickness is a malady showing little or no pathology, except that the mucous membrane of the stomach and intestines shows injection of the blood-vessels and the organs themselves are contracted. Pyers' glands show unusual redness. In the subacute or chronic cases the liver is enlarged, showing a high degree of fatty degeneration. The central veins are dilated and filled with blood, and the bile-ducts are compressed.

SECTION XII: DISEASES OF THE ENDOCRINE GLANDS

CHAPTER I

DISEASES OF THE ADRENALS, THYMUS, PINEAL, OVARIES AND TESTICLES

By Louis T. de M. Sajous, M.D.

Diseases of the adrenals, p. 132:—General anatomy and physiology, p. 132—Functional hypoadrenia, p. 141:—Definition, p. 141; Symptomatology and etiology, p. 141; Diagnosis, p. 147; Treatment, p. 147; Pathology, p. 149—Terminal hypoadrenia, p. 150:—Definition, p. 150; Symptomatology and etiology, p. 150; Association with other diseases, p. 151; Diagnosis, p. 152; Treatment, p. 152; Pathology, p. 154—Addison's disease (chronic progressive hypoadrenia), p. 154:—Definition, p. 154; Etiology, p. 154; Symptomatology, p. 155; Diagnosis, p. 157; Treatment, p. 157; Prognosis, p. 159—Hyperadrenia and adrenal hemorrhage, p. 159:—Etiology, p. 159; Symptomatology, p. 160; Diagnosis, p. 160; Treatment, p. 161; Pathology, p. 161—Hematoma of the adrenals, p. 161:—Etiology, p. 161—Symptomatology, p. 161; Diagnosis, p. 162; Treatment, p. 162; Pathology, p. 162—Hypernephroma, p. 162:—Symptomatology, p. 162; Diagnosis, p. 163; Treatment, p. 163; Pathology, p. 163—Tumors of the adrenals, p. 164:—Malignant tumors, p. 164:—Symptomatology, p. 164; Diagnosis, p. 164; Treatment, p. 165—Benign tumors, p. 165:—Symptomatology, p. 165; Diagnosis, p. 165; Treatment, p. 165.
Diseases of the thymus, p. 165:—General anatomy and physiology, p. 165—Thymus insufficiency (Hypothymia), p. 167:—Mongolian idiocy, p. 169:—Etiology, p. 169; Symptomatology, p. 169; Treatment, p. 169; Pathology, p. 170—The thymus in backward children, p. 170:—Etiology, p. 170; Treatment, p. 170—Thymus hypertrophy, p. 171:—Etiology and pathogenesis, p. 171; Symptomatology, p. 172; Diagnosis, p. 173; Treatment, p. 174; Pathology, p. 175.
Diseases of the pineal gland, p. 176:—General anatomy and physiology, p. 176—Tumors of the pineal body, p. 177:—Treatment, p. 178—Pineal insufficiency in backward children, p. 178.
Endocrinic disorders of the ovaries, p. 178:—General anatomy and physiology, p. 178—Endocrinic ovarian insufficiency, p. 180:—Etiology, p. 180; Symptomatology, p. 181; Diagnosis, p. 182; Treatment, p. 182—Endocrinic ovarian overactivity, p. 184:—Symptomatology, p. 184; Treatment, p. 184.
Endocrinic disorders of the testicles, p. 185:—General anatomy and physiology, p. 185—Endocrinic testicular insufficiency, p. 186:—Etiology, p. 186; Symptomatology, p. 186; Treatment, p. 187—Endocrinic testicular overactivity, p. 188:—Treatment, p. 189.

DISEASES OF THE ADRENALS

General Anatomy and Physiology.—The columns of cells constituting the medullary or inner portions of the adrenal bodies are separated from capillaries and small veins only by a thin membrane, and are believed to secrete into these vessels a product originally consisting of chromaffin granules, *i. e.*, granules having the property of acquiring a brown coloration when the tissue is fixed in formalin containing a chromate. In the adrenal cortex, on the other hand, the parenchyma cells, while still closely opposed to vascular channels, are arranged more irregularly in spherical or oval groups or anastomosing cords. The most conspicuous secretory product of these cells is a species of lipoid granule, thought to consist mainly of cholesterin esters, and supplemented by other granulations, partly pigmentary, of a more obscure composition.

A striking embryologic contrast is presented by the two portions of the adrenals, the medulla being derived from the same primitive source as the sympathetic nervous system, while the cortex is derived, in common with the kidney in its earliest form, from mesoblastic tissues. Subsidiary chromaffin organs apparently having the same secretory function as the medulla and capable, in some degree, of making up for lacking medullary function where adrenal tissue has been destroyed, exist at numerous points in the body, in part in the vicinity of the kidneys and adrenals themselves, but partly also in distant regions.

Both medulla and cortex receive an abundant vascular and nervous supply. The medulla receives both a separate arterial distribution and blood which has already circulated through the cortex from the outer capsule of the organ. The nerve supply includes both non-medullated and medullated fibers, and is in close relationship with the sympathetic nervous system, of which the adrenal medulla may, in certain respects, be said to form a part.

The physiology of the adrenals has been the subject of numerous investigations which, however, from the standpoint of the purely technical physiologist, have as yet borne but little fruit. According to Swale Vincent,[1] the earlier view of Oliver and Schaefer that the function of the medullary portions of the adrenals is to help maintain the normal blood-pressure and to sustain the tone of the tissues innervated by the sympathetic system is no longer tenable. The experiments of Young and Lehman revealed little, if any, fall in the blood-pressure following ligation of the adrenal veins, although it was clear that under normal conditions adrenin is actually poured out into these veins. Austmann and Halliday, who removed the adrenals and observed the blood-pressure until the animal died, failed to note a more marked influence on the pressure curve than that which would occur under protracted administration of ether. Other recent experimenters have shown that in normal animals very small doses of adrenin tend to lower rather than to raise the blood-pressure.

The so-called antitoxic theory of the function of the adrenals, originally sponsored by Abelous and Langlois, which maintains that the toxic effects of certain substances are counteracted by a product formed in these organs, has apparently likewise failed to stand the test of recent physiological research. A. Marie[2] found that *in vitro* adrenin exerts a powerful neutralizing action upon tetanus toxin, but that when dried adrenal powder is used instead of adrenin, the toxic effects of the poison are retained. The exact significance of these observations concerning the defense against tetanus toxin in the living organism was not ascertained.

Experimentation has increasingly revealed that the introduction of adrenin into the system from the exterior is capable of producing, according to the varying circumstances and routes of administration, numerous different effects upon separate structures of the body. Gruber[3] has shown, in animals, that small doses of adrenin cause active dilatation of the blood-vessels in the muscles. According to Cannon and his co-workers, the adrenal secretion is capable of opening up for prompt use the store-houses of sugar in different parts of the body when the system is in need of an unusual quantity of nutriment, *e. g.*, when the muscles are called upon to perform an increased amount of mechanical work. It is well known that full doses of adrenin, when introduced rapidly into the circulation, cause a pronounced rise in blood-pressure, due to constriction of the unstriped muscular tissue of the arterioles. While Gunning[4] found that adrenin given intravenously inhibits the flow of urine, Addis, Barnett, and Shevky[5] observed an increase in the urea-excreting activity of the kidneys when adrenin was injected *subcutaneously* into rabbits. Loeper and Verpy,[6] in experiments on 8 standardized subjects, found that adrenin increases both the total and free hydrochloric acid in the stomach and accelerates the passage of food through this organ, increasing gastric motility in hypotonic subjects, but operating as a sedative in the presence of excessively frequent and intense contractions. Gruber and Kretschmer[7] found, in perfusion experiments on muscle-tissue, that adrenin is capable of increasing the height of contraction and the irritability of a fatigued muscle, whether this fatigue be due to actual muscular work or to the perfusion of fatigue substances such as sarcolactic acid, lactic acid, and acid potassium phosphate. Adrenin in certain amounts has been found to inhibit the contractions of excised intestinal muscle-tissue, but in minute quantities it is thought instead to increase these contractions, and, according to Hartman, Kilborn, and Fraser,[8] constriction of the intestine is sometimes produced by adrenin acting upon the superior mesenteric and dorsal root ganglia.

On the whole, these and other isolated observations of the effect of adrenin on various structures in the body have taught, as physiologists themselves admit, little or nothing concerning the actual functions of the adrenals in the animal organism. Even Cannon's theory of the adrenals as emergency organs, whereby in times of stress the digestive processes are temporarily inhibited and the full energies of the system rendered available for motor action, no longer meets with general approval.

This pessimistic attitude—well expressed by the statement of Dr. W. S. Halstead, of Johns Hopkins, that "it must be evident to every one that there reigns the greatest confusion on the subject of the functions of the glands of internal secretion"—becomes unwarranted, however, when the apparently irreconcilable experimental results reviewed are interpreted in the light of functions attributed to the adrenals by the author's father, Dr. C. E. de M. Sajous (to whom we will hereafter refer, for brevity's sake, as Sajous, Sr.), which, as will now be shown, encompass and explain them all.

A comprehensive analysis of all data available at the time: clinical, physiological, histological, pathological, etc., first published in 1903, by Sajous, Sr., led him to conclude that the adrenals actually do carry on a function of major importance, which is related to pulmonary and general tissue respiration and to metabolism. His conception of this function, constituting what has been termed the "respiration theory" of the rôle of the adrenals, rests upon five chief lines of argument, *viz.*, the phenomena of Addison's disease, the observations of adrenal lesions in acute diseases, the manifestations resulting from certain adrenal tumors, in particular hypernephroma, the effects of large adrenal grafts, and the prevailing unsettled state of physiological knowledge concerning respiration and metabolism.

The Addisonian syndrome, the leading symptoms of which are progressive asthenia, low blood-pressure, weak heart action, hypothermia, and dyspnea, in itself suggests that the underlying functional disturbance is one having to do with the immediately vital processes in the tissues, *i. e.*, with the maintenance of tissue life through the influence of respiration. Vomiting, diarrhea and, in cases of sufficient duration, bronzing, are probably secondary manifestations resulting ultimately from the same fundamental disturbance.

Similar symptoms, accompanied by a tendency to syncope and heart-failure, but with absence of bronzing, have been frequently reported in severe cases of certain infectious diseases, such as diphtheria, scarlet fever, malignant endocarditis, typhoid fever, and pneumonia. That these symptoms actually result from impaired functioning of the adrenals is suggested by the postmortem findings in cases of this type terminating fatally, such findings ranging from a pronounced reduction of the adrenin stored in the gland, with disappearance of the characteristic chromaffin reaction, to manifest interstitial hemorrhages in the adrenals, sometimes so marked as to indicate an actual "apoplexy" of these organs, with subsequent sudden death. Apparently any unusual strain upon the organism in general which requires it to resist infection or intoxication or to perform motor acts with all its power for any considerable period of time entails such a demand upon the adrenin-forming or adrenin-discharging capacity of the adrenals that no residuum can persist in the tissues of the adrenal medulla to give a positive chromaffin test. Kramer,[9] studying the content of adrenin in infants' blood and adrenals under varying circumstances, found that in intoxications due to faulty feeding or to other conditions there is an absence of adrenin in the adrenals. There was also found to be an absence or a subnormal amount of adrenin in premature infants. D. T. Harris,[10] in view of the extreme prostration characteristic of the influenza epidemic of 1918, with marked weakening of the pulse and "loss of physiological resistance," was led to investigate the condition of the adrenals; and at the autopsy of an influenza case, he found the left adrenal soft, diffluent and congested, while the heart, spleen, liver and kidneys were normal. Histological examination of the affected adrenal revealed multiple hemorrhages in the medulla extending into the zona reticulata of the cortex, together with edema of the cells of both medulla and cortex.

While the probability must be admitted that under some conditions a diminution or absence of adrenin in the adrenals may be the result of hypofunction of these glands—possibly due to some toxic action upon them—rather than of exhaustion of adrenin (still being produced in normal amount), by reason of an unusual demand for it in the system at large, the fact remains that discharges of adrenin such as would exhaust the accommodations of this substance in the glands are known to occur under various conditions of unusual stress, nervous excitement, or drug action. The recognized relationship of destruction of adrenal tissue, and consequently of diminution of adrenal function, to Addison's disease strongly suggests that it is a normal rôle of the adrenals to counteract such conditions of general enfeeblement as are manifested in the Addisonian symptoms of extreme adynamia, weakening of the heart action and low blood-pressure, dyspnea, and subnormal temperature. The beneficial effects of adrenin or of more complete adrenal products in conditions in which such symptoms as these occur tend to confirm the existence of a normal relationship between adrenal activity and the maintenance of muscular, including circulatory, power and of adequate heat-giving oxidation.

The third factor upon which Sajous, Sr.'s conception of the importance of the functional rôle of the adrenals is based bears upon the clinical effects of tumors consisting of adrenal tissue, *viz.*, the hypernephromata. These growths, which develop from adrenal tissue, either in the kidneys or in the adrenals themselves—sometimes also in the walls of blood-vessels or in other tissues—consist, partly at least, of either or both cortical and chromaffin or medullary adrenal tissue. Abnormally rapid body growth frequently occurs where such tumors develop between the first and eighth years of life, as is often the case with the true adrenal type of hypernephroma. Thus, in a girl of seven years, suffering from adrenal tumor, reported by Owen Richards,[11] the development resulting from the effects of the tumor was such that, some distance away, the patient resembled a woman of twenty years.

Again, an important influence of the adrenals upon the economy is suggested by the powerful effects that have been noted after the transplantation of large adrenal grafts on human subjects. In a case reported by Bra,[12] in which the adrenals of a dog were engrafted in the cellular tissue of a child, the latter died in three days. Two cases were similarly lost by Jaboulay [13] within twenty-four hours after the same procedure. Especially noteworthy, finally, is the "formidable hyperthermia" or temperature rise noted by Courmont [14] in a case of adrenal grafting, in the absence of any infection of the operative wound. Such an observation as this, in common with the clinical manifestations already referred to, suggests a definite influence of adrenal tissue activity upon the processes of oxidation in the body in general.

On the whole, the facts thus far adduced appear, in the light of Sajous, Sr.'s view, to indicate that the adrenals, apart from an influence on nutrition and general development, possess some function having to do with respiration. In this connection there may be brought forward a fifth feature, *viz.*, the uncertainty still prevailing as to the physiology of the respiratory process from its chemical side. To account for the process of respiration in the lungs, the need has been pointed out, *e. g.*, by Bohr and Henriques,[15] of a substance "having greater avidity for oxygen than the blood itself," or, as they define it, of "a kind of internal secretion." This conception forms the chief feature of what is termed the "secretory theory," of oxygen absorption in the lungs. According to Pembrey,[16] more recently acquired evidence has, to an increasing degree, afforded support to this secretory theory, while experimentation by a number of well-known physiologists, including Bohr,[17] Haldane and Lorrain Smith,[18] and Vaughan Harley,[19] has seriously invalidated the formerly accredited "diffusion theory" of respiration.

The chain of evidence upon which Sajous, Sr., bases his opinion that it is the adrenal secretion which fulfills the respiratory function hitherto unaccounted for is as follows:

1. The adrenal secretion enters the venous blood stream by passing through the adrenal veins into the inferior vena cava.

The truth of this proposition is supported, in the first place, by the observation of Gottschau,[20] Manasse,[21] Aulde [22] and Stilling,[23] who traced hyaline granules representing the adrenal secretion from the adrenal tissue into the adrenal veins. The identity of these granules with the secretion of the adrenals was shown by Stoerk and v. Haberer,[24] who found intracellular granules, manifestly constituting the well-known chromaffin material in these organs, diffusing out of these cells into the vascular channels in the form of a highly refractile, yellowish-brown mucoid material. Again, Pfaundler [25] demonstrated the granules previously described by Gottschau actually passing along the adrenal veins into the vena cava. Finally, Cybulski and Szymonowicz,[26] and subsequently many other investigators, showed that blood from the inferior vena cava above the entrance of the adrenal veins, when injected into other animals, induced the rise of blood-pressure characteristic of the adrenal active principle, while venous blood obtained from other segments of the circulatory system failed to produce this effect.

2. The adrenal secretion reaches the pulmonary air-vesicles, and

there plays a rôle in the absorption of oxygen from the air, which could not otherwise be completely accounted for.

Paul Bert[27] showed experimentally that oxygen continues to be absorbed by the blood circulating in the lungs, even when the pressure of this gas in the air-vesicles has been reduced to almost *nil,* while Müller found that in a strangulated animal the air in the lungs becomes exhausted of all its oxygen. An active absorbing agency in the pulmonary blood is thus suggested which, according to the view of Bohr and Henriques already mentioned, consists of "a kind of internal secretion." This circumstance, together with the fact that the adrenal product, a reducing substance, necessarily and very promptly passes from the inferior vena cava into the pulmonary circulation, definitely suggests a participation of this product in the oxygen-absorbing process referred to.

3. The affinity of the adrenal secretion for oxygen causes it, upon reaching the pulmonary alveoli, to take part in the absorption of this gas and to promote the oxygen exchange.

Numerous investigators, including Vulpian[28] and Cybulski[29] have pointed out the reducing properties of the adrenal principle *in vitro.* Oxygen-yielding compounds, or the atmospheric oxygen itself, soon cause it to lose its affinity for oxygen, this affinity having evidently been satisfied through absorption of oxygen. Battelli[30] showed that when contact of air with adrenin is prevented, the latter preserves its reducing property indefinitely. Finally, M. L. Menten,[31] from careful physiological experiments, concluded that adrenin "does particularly affect the oxygen exchange in that organ" (the lung).

4. The adrenal secretion actively influences the respiratory process from the standpoint of oxygen intake and the output of carbon dioxid.

Byelaventz[32] found experimentally that adrenin increases the gaseous interchanges, while Bernstein and Falta[33] observed that subcutaneous injections of 1 mg. (1/64 grain) of adrenin produce, in normal individuals, an increase of oxygen consumption, carbon dioxid output, and respiratory quotient. Again, Nice, Rock, and Courtright[34] confirmed the observation of earlier investigators that the injection of adrenin causes an increase in the depth of respiration, and added to it the conclusion that such an increase of depth occurs whether the principle be introduced in minute amounts, which cause a reduction in blood-pressure, or in larger doses, causing a rise.

5. Tissue oxidation is also influenced by the adrenal secretion.

A rise of body temperature was shown by Oliver and Schaefer[35] to occur when an aqueous extract of fresh adrenal substance was injected subcutaneously into dogs. Reichert[36] observed a rise of temperature of 1° C. (1.8° F.) accompanied by increased metabolism, when adrenalin was injected into dogs in doses of 1 mg. (1/64 grain) per kilo of body weight. According to Lépine,[37] a rise of temperature regularly follows the rise of blood-pressure induced by adrenal extract administered in therapeutic doses. Furthermore, it has been observed that when the adrenals are experimentally removed, a progressive decline in the temperature follows.

6. It is by becoming a constituent of the hemoglobin that the adrenal secretion takes part in tissue oxidation and metabolism.

The observations of Menten and Crile[38] showed that the adrenal secretion is capable of endowing hemoglobin with oxygen-carrying power. Blood from the adrenal vein was found invariably to take on a bright red, arterial color in from one to twenty minutes after dilution with saline solution, whereas blood from other organs, similarly treated, failed to present this modification. The change of color was found by means of the spectroscope to be due to an increased formation of oxyhemoglobin. Addition of adrenin to diluted human venous blood was also noticed by Menten[39] to produce an increase in the intensity of the oxyhemoglobin absorption bands. The similarity of the spectra of blood from the adrenal vein and of venous blood to which adrenin has been added "is unquestionably very strong evidence," according to this experimenter, "that it is adrenalin which is responsible for the increased amount of oxyhemoglobin found in the adrenal vein blood."

The objection might conceivably be raised against the "respiratory theory" of the adrenal function, that the quantity of adrenin circulating in the blood is too small to meet the requirements of this theory. But Stewart and Rogoff,[40] in a study of the spontaneous liberation of the adrenal secretion in the cat, found that it varied from 0.0003 to 0.001 gram a minute per kilo of the animal's weight. At this rate, a man weighing 70 kilos would receive in his blood from 1.26 to 4.20 c.c. (20-67.3 minims) of adrenal secretion per hour, *i.e.*, over 30 to 100 c.c. (1-3.38 fluidounces) in the twenty-four hours—ample to meet the needs of oxygenation and metabolism.

The strength of Sajous, Sr.'s position in this connection further suggests itself in view of the ease with which his "respiration theory," considered as a fundamental function, harmonizes all apparently discordant observations of other investigators. Briefly, it explains the following facts: (1) that adrenin in large doses sustains the tone of the vascular system by accelerating oxygenation and metabolism in the muscular coats of all vessels, including their myoneural junctions; (2) that small doses lower the blood-pressure because, by first increasing oxygenation and metabolism in the smallest vessels, the vasa vasorum, they reduce the arterial supply of the muscular coats of all vessels and thus cause their dilatation; (3) that adrenin promotes all antitoxic functions by accelerating oxygenation and metabolism in all tissues taking part in those functions; (4) that in keeping with Cannon's emergency theory, excitement, fear, etc., cause excessive adrenal activity, the increased needs for adequate defense requiring a corresponding increase of oxygenation and metabolism; (5) that by increasing oxygenation and metabolism, adrenin can increase urea excretion, the secretion of hydrochloric acid, gastric motility and the contractility of fatigued muscles; (6) that large doses of adrenin can inhibit contraction of the intestinal muscles by causing constriction of their arteries, thus inhibiting their supply of arterial blood; (7) that minute doses promote the oxygenation of the muscularis intestinalis, favoring peristalsis.

The observation that removal of the adrenals or ligation of the adrenal veins failed to cause an early and material lowering of the blood-pressure is explained by the residual hemoglobin in the whole blood, and by the fact that the adrenals represent only a portion of the chromaffin system, which includes the entire sympathetic system, adrenal rests in various organs and several accessory structures. These results, moreover, are controverted by many experiments on record in which the blood-pressure and temperature steadily declined until death occurred.

Again, were the adrenal principle to operate after the manner of an enzyme or ferment, its presence in the circulation in but small amounts, in spite of the important physiologic rôle ascribed to it, might readily be understood. That the principle actually does operate as a ferment is indicated by Menten's observation of modifications in its activity taking place under the influence of temperature changes within fixed limits—a peculiarity of enzymes as a class. Again, the oxidizing ferment observed by Bunge and Schmiedeberg,[41] Jaquet,[42] Abelous and Biarnès[43] in the animal humors shows heat reactions in many respects similar to those of adrenin. As far back as 1853, Traube concluded that hemoglobin could not perform its characteristic function without the assistance of a catalyst, *i. e.*, in this case a substance having the power to hoard oxygen and also to crowd it, as it were, upon the body tissues as an "accelerator." Jolles[44] referred to the activity of the blood as a catalyst, which activity he found to correspond to the number of erythrocytes it contained. Poehl,[45] in turn, also found the adrenal principle to be a catalyst.

Were the above evidence to the effect that the adrenal principle acts as a ferment to be accepted as sufficient, the requirement of but small amounts of this principle to carry on the important respiratory function referred to would no longer appear surprising. Enzymes having fundamentally the property of causing chemical rearrangements in other materials without being themselves consumed in the process, the adrenals, and other chromaffin tissues, would be required only to make good minor losses of the enzyme, the accumulated residuum of which would be preserved as the oxygen-carrying agency of the hemoglobin and be constantly re-used, after having lost its identity as adrenin.

Similar considerations apply in controverting another objection which might possibly be made to the respiratory theory of adrenal function, *viz.*, that the quantity of adrenin necessary to carry on the asserted respiratory process would be sufficiently large to cause death by paralysis of the gastro-intestinal canal. From the start the fallacy of this objection seems to be indicated in the accepted teaching of physiologists that "adrenin circulating in the blood is rapidly destroyed" by oxidation. Such being the case, the adrenal product, after passing through the entire pulmonary circulation, with the contact with oxygen afforded in the lungs, and also through the left heart and the arterial channels conveying the blood to the walls of the gastro-intestinal tract, cannot be expected to exert much of an inhibitory action upon reaching the muscular tissue of this tract. Furthermore, the clinical experience of Sajous, Sr., has thoroughly convinced him that gastric or intestinal peristalsis is not arrested when either adrenin or dried adrenal gland is given by mouth or when the former agent is injected hypodermatically, intramuscularly, or intrarectally during brief or prolonged periods, in therapeutic dosage. In many cases in which from 3 to 7 minims (0.18 to 0.42 c.c.) of 1:1000 adrenin solution were given by mouth for several weeks the drug appeared only to serve as a tonic and to increase the appetite. A medical patient suffering from asthma wrote that he had used adrenin at least once a day and sometimes twice a day, hypodermatically, in doses of 10 minims (0.60 c.c.) of the 1 :1000 solution, for several months. His blood-pressure rose from 130 to 180, he lost flesh, and was apprehensive of a permanent rise in pressure. Yet no gastric disturbance was produced.

On the whole, the facts presented above would seem to substantiate in a considerable measure the view of Sajous, Sr., that the adrenals play an important functional rôle, in part at least, respiratory, in the animal organism, and, correspondingly, to indicate that where the functional integrity of the adrenals is impaired through acute or chronic disease, widespread disturbances in the body at large are to be expected.

That nervous influences may play a rôle in augmenting adrenal activity is suggested by the experiments of Mackenzie,[46] who found that an increased secretion of adrenin followed the application of nervous stimuli, especially to the sympathetic system—piqûre or excitation of the splanchnic nerves. The adrenal function may also be influenced, according to Sajous, Sr.,[47] by the pituitary body, from which he has traced a nervous pathway leading directly down to the adrenals. Sympathetic (vasoconstrictor) activity and adrenin secretion have been linked together by G. F. Gaskell[48] as regulators of the blood-vessels in general, in view of the well-known similarity in embryonic origin of the sympathetic nervous system and the chromaffin cells.

The adrenals apparently also take part in the production of tonic effect on the heart by certain drugs. Many years ago Sajous, Sr.,[49] pointed out the probability of this, and more recently Gley,[50] studying the pharmacologic action of nicotin and anagyrin, was led definitely to ascribe the effects of these agents on the heart to a stimulating action on the adrenals. Cannon and De La Paz had already observed experimentally that nicotin was capable of inducing a discharge of adrenin from the adrenals. Another functional relationship was suggested by observations of Cannon and Cattell,[51] who found that the administration of small amounts of adrenin—or stimulation of the splanchnic nerves leading to the adrenals—caused increased activity of the thyroid gland. This would tend to confirm the view of Sajous, Sr., recorded a number of years before, that the adrenals, when stimulated, increase general metabolism indirectly through excitation of the thyroid.

A review of the present knowledge of the physiology of the adrenals would not be complete without special mention of the cortical portions of these organs, which have been considered by some to be even more essential to life than the medullary. Wheeler and Vincent[52] have reported instances of experimental animals surviving, without symptoms, complete or almost complete destruction of the medullary tissues. While the question suggests itself whether the survival of these animals may not have been due to the presence of unaffected bits of chromaffin tissue situated elsewhere, the authors referred to seem inclined to ascribe death following total adrenalectomy either to the removal of the cortical portions alone or to the combined removal of the cortical and medullary portions, removal of the latter alone not necessarily proving fatal according to their observations. Voegtlin and Macht[53] found in the adrenal cortex a substance possessing an action resembling that of digitalis, and Iscovesco[54] claimed to have detected in it a cardiotonic lipoid. Again, it has long been believed that the adrenal cortices are capable of exerting a pronounced stimulating influence upon the essential organs of reproduction, or at least that they are in some manner functionally associated with the development of the sexual organs. Evidence has been collected by Vincent[55] to the effect that when tumors of the cortical tissue occur in the female, an accentuation of male secondary sexual characteristics is exhibited, while at the same time the internal generative organs show a hypoplastic condition. Enlargement of the adrenal cortex during breeding and pregnancy is another factor suggesting a genital relationship of the tissue. Stimulation of the growth of the testes seems to result from feeding young animals adrenal gland substance. Finally, considerable clinical evidence has been recorded to the effect that these same influences on the part of the cortex apply likewise in the case of man, this portion of the adrenals exerting a marked effect upon the sex characters and being involved in the causation of a premature development of the sexual organs, with unusual hirsuties, etc. It seems not unlikely, however, that the medullary portion of the adrenals may itself assist in the production of these changes by increasing the general oxidation.

FUNCTIONAL HYPOADRENIA

Definition.—A state of reduced physiological activity of the adrenals existing in the absence of any definite organic disease, and due to one of a number of different causes, such as hypoplasia, old age, fatigue, starvation, and other debilitating influences.

Symptomatology and Etiology.—The symptoms resulting from this disturbance vary to some extent according to the cause and the age of the individual.

In childhood, the symptoms due to a hypoplastic condition of the adrenals begin to appear after weaning, *i.e.*, when the immunizing substances transferred to the infant through the mother's milk are no longer available to it and the task of maintaining adequate resisting power and general vitality falls entirely upon the protective organs and metabolism-regulating structures in the system of the child itself.

The child suffering from hypoadrenia is of the type exhibiting pallor, a pasty aspect of the skin, a flabby musculature, lack of circulatory tonicity or a relatively feeble cardiac function—as shown by a tendency to cold hands and feet—a capricious or deficient appetite, an unusual vulnerability to infections, and sometimes a reduction in body-weight below the normal for the child's age. While the poor circulation and pallor are doubtless in a considerable measure due to hypofunction of the medullary portions of the adrenals, it becomes a question—in view of the recent experimental as well as clinical emphasis which has been placed upon the cortex—whether the action of this portion of the adrenals may not also account for part of the disturbance in these cases. The circulatory condition which apparently exists is one of relative dilatation of the splanchnic vessels and reduced contractile power of the heart, the result being, in a general way, a recession of the blood from the skin to the central portions of the body, with consequent pallor of the surface—a condition similar to that obtaining during chloroform anesthesia, although of course less pronounced.

Among young or middle-aged adults, functional hypoadrenia through actual hypoplasia of the adrenals is also a possibility, and as in the case of children, relative weakness of circulation is one of its important manifestations. In addition, however, there may be a tendency toward excessive deposition of fat, owing to reduced oxidizing power, and likewise toward the appearance of bronze spots, which are somewhat suggestive of adrenal impairment. In some instances, emaciation is a prominent feature. An asthenia similar to that of Addison's disease, although not as marked, may be noted. Not only is the general muscular tone diminished under these conditions, in harmony with the demonstration of the influence of the adrenals over muscular tone by Oliver and Schaefer many years ago, but the fatigability of the muscles is greatly increased. Pallor and an abnormal susceptibility of the individual to cold and exposure, particularly as regards the intestines, are also common accompaniments of this condition.

In old age, asthenia, evidences of auto-intoxication, bronze spots, and other manifestations similar to those already mentioned with reference to earlier periods may result from a special change in the adrenals somewhat peculiar to this time of life, *viz.*, senile degeneration and fibrosis. The researches of Landau, von Kölliker, Minervini, Dostojewski, and others, have definitely shown that connective tissue infiltration, fat deposition, and reduction in size of the adrenals are common results of the action of advanced age upon these organs. According to Lorand,[56] impairment of the endocrine glands as a group, including the adrenals, is one of the underlying factors in senescence, and the unfavorable reaction upon these glands of hygienic, dietetic, and other common errors of living, constitutes an important reason for the oncoming of senility at the age of sixty or seventy years instead of at ninety or one hundred.

Physical fatigue is a frequent cause of temporary functional hypoadrenia. During the European War, many cases of rather persistent physical depression, with a tendency toward subnormal temperature. were attributed to exhaustion of the adrenals. To all appearances, these glands were called upon during exertion to discharge an unusual amount of their secretion, and when a certain limit had been reached, function on their part was markedly reduced or completely interrupted, and restoration of function was rendered possible only by a relatively prolonged period of rest. What the ultimate effect of continuous severe exertion upon the adrenals may be is illustrated by an instance reported by Carl,[57] in which these organs were found, in the case of a bicyclist who had died as a result of overexertion, to be free of chromaffin substance. The induction of strychnin-convulsions in frogs was found by Carl to have the same effect on the adrenals in these animals, the chromaffin reaction being apparently counteracted by excessive consumption of the adrenal secretion during the convulsions. That not merely sudden violence, but also an actual exhaustion from continuous overstrain, is required to annul the chromaffin content of the adrenals is indicated by the recent work of Sampaio,[58] who employed tests of the adrenin content of the cortex of the adrenals after death as a means of ascertaining whether or not death had taken place suddenly. Instances of sudden death resulting from such agencies as suicide, and firearms, phenol-poisoning, drowning, and rupture of the middle meningeal artery or thoracic aneurysm, showed a high content of adrenin in the adrenal cortices—the author having learned to expect such a high content in all "agonal" forms of death—whereas in exhausting chronic disease, *e.g.*, tuberculosis, the adrenin content was found to be very low. Prolonged invalidism, however, did not prove to be a necessary factor in lowering the adrenal content, an important prerequisite, apparently, being the absence of an agonal or violent death. A very low adrenin content was found, for example, in a case of death four days after postpartum hemorrhage. Lucksch,[59] in somewhat similar tests, found the adrenin values to be particularly low in "anomalies of constitution," infectious diseases, and after burns.

During the European War, a considerable mass of literature appeared, dealing with the clinical manifestations of adrenal insufficiency as a result both of physical fatigue and of infectious disease. In many instances, seemingly, preëxisting fatigue predisposed to the appearance of these adrenal manifestations when infection was subsequently added.

One of the best of the contributions made on this subject was that of J. Carles,[60] who encountered 15 cases of presumptive acute adrenal insufficiency among French combatants. In all cases the symptoms came on rapidly. In 8 instances, prolonged fatigue seemed to be the only etiological factor, while, in the remaining 7, infections, or toxic factors, were present, usually occurring after over-exertion had already prepared the way. The exciting factors in these 7 cases comprised: a paroxysm of malaria, typhoid fever, rapid pulmonary tuberculosis, congestion of the lungs, acute gastritis, gassing, and a war wound. In addition, there were 2 cases of Addison's disease of the classic type (but rather rapid in onset), and 2 cases of gastro-intestinal disturbance of the type ascribed by Loeper to adrenal disturbance, and notably improved by adrenal treatment. Brownish discoloration of the skin (melanodermia) was present to varying degrees in each of the 15 cases, and in one-half of the cases the mucous membranes were similarly discolored. In all instances asthenia was the most striking symptom, and mental asthenia was at least as marked as physical asthenia. Muscular action of any kind was performed only with difficulty, prolonged locomotion became an impossibility, and mental asthenia was so pronounced among some of the men that, although of high intelligence and good education, they were unable to read the newspaper, write a letter, or even to think and answer questions promptly. Treatment with adrenal products always brought prompt improvement from this condition. Low blood-pressure was noted in all cases, but this, Carles points out, is a common manifestation in all fatigued fighting men. Headache, lumbar pains, and vomiting were sometimes present. A particularly striking case was that of a soldier who, following physical exhaustion, developed marked melanodermia, pigmented plaques in the mouth, general adynamia, pronounced lowering of blood-pressure, vomiting, lumbar pains, marked loss of weight, and inability to perform any mental work. His condition was so acute that death seemed probable. After three months' treatment, however, his health was sufficiently restored to permit of his following regularly a clerical military occupation. In another similar case, the patient, after treatment, was sent back to the trenches. Recurrence took place, however, after a few weeks, and in this second attack of adrenal insufficiency, treatment was almost without effect. The patient's skin gradually became as dark as that of the colored race, the mucous membranes became deeply pigmented, the patient progressively lost weight, and the cervical lymph-nodes became markedly swollen. This case is taken to indicate that after a man has once had one of these adrenal attacks, he is unfit for further active service as a combatant. The adrenals seem to remain impaired for a considerable time, if, indeed, they are not placed in a permanent state of functional debility. Carles lays some stress also upon the antitoxic function of the adrenals, particularly in connection with the toxic wastes resulting from physical work, the accumulation of which determines fatigue. At first, the adrenals tend to adapt themselves to an excess of work, but if the amount of work imposed is too great, they are soon overwhelmed, and the consequent failure of their antitoxic activity against endogenous poisons involves also their defensive function against exogenous poisons, with the result that the subject is exposed more than usual to any infectious disease—tuberculosis in particular.

The effects of infections on the adrenals will be further considered in the section on Terminal Hypoadrenia. Exogenous intoxication of the adrenals does not occur solely, however, as a consequence of infections, but may also be produced by poisonous chemicals which have been taken into the system. Merklen and Malloizel[61] have recorded a particularly striking case of this type in a munition worker who became poisoned with dinitrophenol. They definitely ascribe the symptoms witnessed to toxic adrenal insufficiency. After the patient had largely recovered from the immediate typical manifestations of dinitrophenol poisoning and had been sent away for convalescence, he developed vomiting, marked asthenia which practically forced him to remain in bed, severe pains in the hypochondriac regions, a pronounced "white line," a reduction of blood-pressure to 85 mm. Hg., and hypothermia, the temperature remaining between 36° C. (96.8° F.) and 37° C. (98.6° F.) for some time and twice even descending to 35° C. (95.0° F.). The urine no longer contained dinitrophenol during this adrenal stage of the illness. After the blood-pressure had reached its low point of 85 mm., it began a very gradual rise again to normal, reaching 145 mm. in the course of about seven weeks. During the same period all the other adrenal manifestations gradually passed off. The conclusion of Merklen and Malloizel that this patient must have had some preëxisting debility of the adrenals, which predisposed them to a toxic functional hypoadrenia, seems warranted. These authors compare the case with others previously recorded in which adrenal debility was indicated by symptoms appearing as a result of chloroform anesthesia, although previous to this special stress no manifestations of adrenal weakness had ever been noticed.

Two special aspects of functional hypoadrenia which were developed during the war are: (1) gastro-intestinal disorders, termed by Loeper "suprarenal dyspepsia," and (2) neurasthenic and psychasthenic manifestations. Loeper[62] observed a number of instances of an incomplete or "fruste" suprarenal disturbance characterized by anorexia, digestive atony, constipation, vomiting, gastric pain, paroxysmal intestinal pain, abnormal sensitiveness of the abdomen, and low blood-pressure. That these disturbances are actually due to functional hypoadrenia is shown, he believes, by the fact that whereas in ordinary dyspeptics the administration of adrenin is without therapeutic effect, in these cases the condition of the patients was promptly "transformed" by it. Under daily injections of moderate amounts of adrenin—ranging from 0.1 to 1 milligram (1/640 to 1/64 grain)—digestive discomforts often disappeared by the third injection; constipation was relieved, appetite returned, an increase in body weight soon occurred, asthenia was overcome, and the blood-pressure rose. All these beneficial effects were rapidly produced by adrenin, although all ordinary remedies for digestive disorders had previously failed. Definite objective evidence of the effect of the treatment seems to have been secured by test-meal, and by *x*-ray methods. The stomach contents showed an appreciable rise in gastric acidity as a result of the use of adrenin, while the *x*-rays revealed a regulating action of the remedy on the motor functions of the stomach and bowel. In the case of 6 patients in whom, before the administration of adrenin, bismuth had only begun to enter the transverse colon at the seventh hour, it was found that after the drug had been given the bismuth reached the rectum by the seventh hour. Loeper ascribes the benefit from adrenin in these cases to a tonic action on the sympathetic system with resulting improvement of secretory activity and nervous control of the gastro-intestinal tract—the adrenin administered presumably making up for the amount of adrenal secretion lost through the temporary functional impairment of these organs, which amount normally sufficed for the proper control and regulation of the stomach and bowel. The fact seems worth noting in this connection that whereas the sympathetic system is commonly regarded as possessing an inhibitory action on the gastro-intestinal tract (the pneumogastric being the accelerator nerve), and adrenin in full laboratory doses exerts a similar action, minute amounts of adrenin have been shown to exert in some respects opposite effects, *e. g.*, they accelerate intestinal motor activity instead of arresting it. The clinical effects noted by Loeper are thus brought into better agreement with facts previously observed in the laboratory. One is thus better enabled to understand the necessity of using only relatively small amounts of adrenin, such as were administered in Loeper's cases. As is well known, excess of adrenin may likewise result in disturbances of the digestive tract. Since the degree of adrenal impairment in functional hypoadrenia must vary in different cases, proper adjustment of dosage would seem to be a necessary factor in yielding optimal results and doubtless such adjustment can at present be procured only by the trial of different amounts in the individual case.

Adrenal psychasthenia has been emphasized by Laignel-Lavastine as being a possible, more or less independent, manifestation of hypoadrenia. According to this author, an actual disturbance of the mind amounting to "anxious melancholia" may even result. Various authors have expressed the belief that so-called "neurasthenia" is a symptom-complex due mainly to some disturbance of the endocrine organs, and have laid especial stress on deficient functioning of the adrenals in this connection. Attention has been called to the fact that the blood-pressure in neurasthenia is generally low as compared with the pressure in the same individuals when they were normal, that the circulation in general is poor, and that vasomoter regulation of blood distribution is impaired. Over ten years ago Sajous, Sr., advanced the same idea from a slightly different aspect, pointing out that neurasthenia is a result of exhaustion of the sympathetic center—which governs the adrenals—and recommended for this condition the use of remedies, including adrenin, which overcome vascular relaxation and loss of propulsive activity of the arterioles, as well as remedies, such as acetanilid, which stimulate the sympathetic center directly. More recently, Kinnear Wilson pointed out the irregular blotches on the skin of the face and neck of the excited neurasthenic, his clammy hand, flushed or pallid features, dilated pupils, and various paresthesias, as being almost self-evidently manifestations of sympathetic disturbance. He thinks that there is no radical distinction between the asthenia of neurasthenia and that of Addison's disease, and finds it difficult to escape the conclusion that deficient function of the chromaffin system, including the adrenals, is responsible for much of the clinical picture of neurasthenia.

Diagnosis.—The diagnosis of functional hypoadrenia is made on the basis of the characteristic symptoms and signs already referred to under Symptoms. Where only a few of these evidences are present the diagnosis may be difficult. In some reported cases, doubt having arisen as to whether or not the two or three suggestive symptoms present were actually due to diminished adrenal function, markedly beneficial effects following the administration of comparatively small doses of adrenal products were relied upon as the main differentiating feature.

A frequently emphasized indication of adrenal weakness is Sergent's "white line phenomenon," the true differentiating value of which is, however, still doubted by some. This sign is elicited by stroking the skin of the abdomen with a blunt object, such as the finger tip. If the test is positive, a white streak appears within a few minutes along the stroke previously made. For a time this becomes increasingly distinct, then remains unchanged for a while, and finally disappears gradually. Lautier and Grégoire,[63] in tests conducted in 228 cases, found the white line present with almost equal frequency in cases with low blood-pressure and with high blood-pressure, and concluded from this that the white line is unrelated to the blood-pressure. Again Baudron[64] found the white line present in 81 out of 100 cases of sick or wounded soldiers, the positive cases including a number of instances of purely local conditions, such as gingivitis and orchitis. The general conclusion of these authors is, however, that the white line is of service in the differential diagnosis of acute adrenal insufficiency from febrile conditions of meningeal, thoracic, or abdominal origin. When this sign occurs in such infections as grip and rheumatic fever it implies, according to Baudron, some degree of asthenia and hypotension, with slight adrenal impairment. When, on the other hand, it is present with a mere local condition, it is simply a coincidence or is the result of some temporary derangement of vasomotor equilibrium. Ravaut and Krolunitsky,[65] after a study of numerous cases, have also expressed themselves in favor of Sergent's own view of the importance of the sign as an indication of diminished adrenal functioning.

Treatment.—Prophylaxis.—Prophylactic treatment of functional hypoadrenia is in some respects practicable. Thus, in infancy and childhood, factors which threaten the integrity and proper development of the adrenals, such as **infections, intoxication,** and **malnutrition,** should be **avoided** in so far as possible by proper precautions. **Breast-feeding** of infants should be **encouraged,** for immunizing substances have been shown to be transmitted with maternal milk to the offspring. If artificial feeding is resorted to, the protective organs of the body, including the adrenals, not yet prepared to assume their functions in this direction, may be overburdened during their developmental period, and a weakness in these organs may result which will leave its mark on the individual throughout life. After weaning, an important prophylactic measure is the use of milk known to be **free from contamination** with pathogenic bacteria. In older children, proper **hygiene at school and in the home,** with due municipal health supervision in order to minimize the incidence of infectious diseases, especially those of the more serious order, such as diphtheria, scarlet fever, and typhoid fever, are obviously of marked significance in this type of prophylaxis.

CURATIVE TREATMENT.—Where functional hypoadrenia is already an established condition, treatment may consist either in **stimulating the adrenals** to increased activity or in making good the deficit in adrenal secretion. For the former purpose, Sajous, Sr., recommends **mercury biniodid** or **calomel**; **arsenic** and **digitalis** may also be of service. The second object is fulfilled in prescribing, for feeble children, ten or twelve years of age, a capsule containing **dried thyroid gland,** 1 grain (0.065 gram), **dried suprarenal gland,** 2 grains (0.130 gram) and **Blaud's mass,** 1 grain (0.065 gram) to be taken three times daily during meals. **Strychnin** in small doses may also be included if the nervous reflex functions seem sluggish or the circulation feeble. **Meats** and **milk** are of particular value in the diet of these cases.

In adults functional hypoadrenia, unless it has been present since childhood, usually comes on as a result of physical or mental overstrain, or from infection or intoxication, and is therefore most rationally treated by complete **rest,** by measures calculated to shorten and attenuate the harmful effects of infection, or by **removal** of the **toxic factor.** As already shown under Symptomatology, acute adrenal deficiency is gradually recovered from under a régime of absolute rest; the recovery, however, is not always quite complete, the patient remaining sensitive to overstrain for an indefinite period. In acute functional hypoadrenia of alarming intensity, the administration of **adrenal preparations** is, according to Carles,[66] capable of actually saving life, supplying the essential amount of secretion until at least partial return of adrenal function can take place. In less serious instances, it will at least in part relieve the symptoms resulting from deficient secretion, may also conceivably hasten the return of adrenal activity by its very presence in the body fluids (homostimulation), and may temporarily assist the patient in combating infection. A rather careful study of the best procedures in carrying out adrenal medication in these cases has been made by Josué.[67] **Adrenin** was found effectual when given by mouth in the dosage of from 1 to 4 or even 5 c.c. (16-64.8 minims, or 1.35 fluidrams) of the 1:1000 solution a day, in divided amounts. The "slow absorption" method recommended by him, when the hypodermic route is to be used, consists in injecting under the skin from 250 to 500 c.c. (8.44 to 16.9 fluidounces) of normal saline solution to which 1 mil of adrenin solution and 0.01 gram (1/6 grain) of procain have just been added. The amount of adrenin solution given in a day by this method ranges from 0.5 to 2 mils; 0.5 mil should be considered the maximum single dose. In some instances, Josué found extracts of the whole adrenal gland to be superior to adrenin. He gave the whole adrenal either by mouth in the daily dosage of from 0.2 to 0.4 gram (3.086 to 6 grains) or by hypodermic injections of 0.1 gram (1.543 grains) daily.

Somewhat similar treatment was instituted by A. Satre[68] in cases of apparent acute adrenal insufficiency following the injection of antityphoid vaccine. Not infrequently this condition occurred in the case of soldiers who had shortly before been greatly fatigued by long marches or other heavy physical work. Sergent's symptomatic triad of adrenal inadequacy, *viz.*, the white line, pronounced reduction of blood-pressure, and asthenia, so marked that the subject could hardly move or think, was always present in these cases. Vomiting and abdominal pain were likewise present almost constantly. Other manifestations were: rigor, fever with restlessness, or hypothermia, headache, vertigo and a tendency to syncope, pallor or cyanosis, rapid respiration, feeble or even absent pulse, hiccough, scanty urine, and diarrhea. These effects came on an hour or two—less frequently five or six hours—after the injection of vaccine, and continued for two or three days or sometimes longer, up to a week, after which restoration to normal took place gradually, unless hastened by treatment with adrenin. In the treatment, Satre administered this agent either intramuscularly, by mouth, or by both of these routes at once, as Sergent recently recommended. It was found best to give the drug in moderate but frequently repeated doses; not only were unpleasant effects such as nausea, dizziness, heat flashes, and tremor thus avoided, but the drug action was kept up, and as much as 4, 5, 6, and even 9 mg. (1/16, 1/12, 1/10, 9/64 grain) of adrenin a day could be given. Only 0.5 mg. (1/120 grain) should, according to Satre, be injected at a time at one point. To slow down its absorption, the 1:1000 adrenin solution may advantageously be given, freely diluted in normal saline solution—the latter previously sterilized. Occasionally, where free and prolonged injection of saline solution was impracticable, enteroclysis of normal saline solution containing adrenin may be carried out by the drop-method. Satre adheres to the view that the administration of the whole adrenal gland will make up for a deficiency of the antitoxic function of the adrenals, whereas the action of pure adrenin is confined rather to overcoming circulatory impairment. In some cases in which intoxication seemed particularly profound, therefore, he gave from 1.5 to 5 grams (23.14 to 77.16 grains) of **fresh adrenal gland**, or from 1 to 3 grams (15.43 to 46.30 grains) of **desiccated whole extract** daily, in cachets each containing 0.30 gram (4.63 grains). Marked benefit is stated to have resulted in all these cases from the treatment with adrenal products.

In the case of adults exhibiting continuous functional hypoadrenia, **mercury** in small doses may be given to stimulate the organs concerned, as has been already mentioned in connection with the treatment of functional hypoadrenia in children.

In hypoadrenia assuming the neurasthenic form, and in so-called "adrenal dyspepsia," adrenin or adrenal gland is indicated.

Pathology.—The term "functional hypoadrenia" excludes any definite pathological changes in the adrenals when the word "functional" is taken in its generally accepted significance, *i.e.*, non-organic. Diminution or absence of chromaffinity may, however, be considered merely a functional disturbance, and even more or less definite cellular changes doubtless do occur in some of the varieties of cases discussed in the preceding section. Particularly is this evident in senile hypoadrenia, in which different observers have found distinct modifications in the adrenal tissues as compared with those of young or middle-aged adults. Thus Landau,[69] having made corrosion preparations of the veins of the adrenals from young adults and from persons aged eighty years or more, found the vascular system of these organs markedly reduced and shrunken in the latter group of individuals. Dostojewski noted a marked reduction in size of the adrenals in the aged, while Minervini[70] found the adrenal medulla fibrotic in the bodies of old subjects and Hultgren and Andersson noted fibrosis between the medullary and cortical layers in aged animals. Other observers have called attention to the increasing deposition of fat in the cortex of the adrenals as age advances.

Apart from these manifest tissue changes in senile hypoadrenia, our knowledge of the actual conditions of the tissues in other forms of hypoadrenia is scanty. These conditions probably vary considerably in different cases. Doubtless in many instances the difficulty consists merely in an exhaustion of adrenal secretion through excessive demand or excitation, and a period of rest is all that is required to overcome the "functional" deficiency. It is readily conceivable that during stress such hyperemia in the adrenal tissues may occur as to induce actual blood stasis and reduction of nutrition, with consequent diminution or arrest of secretion on the part of the adrenal parenchyma. Again, preëxisting adrenal weakness through hypoplasia or acquired degenerative changes of various sorts may not in itself result in symptoms, unusual functional demand being necessary to bring on such symptoms. The condition in such cases may be termed a *latent functional hypoadrenia,* the relatively small amount of healthy adrenal tissue remaining being sufficient for ordinary needs but being overwhelmed when any additional work is demanded of it. An illustration of such a case is that recently reported by H. M. Rashbrook and F. W. Carter[71] as an instance of "hypoadrenia simulating intestinal obstruction." After exhibiting for about five weeks, as a result of active military service, abdominal pain, vomiting, constipation, and a tendency to collapse, this patient succumbed, and at the autopsy the glandular cells of the adrenals were found for the most part replaced by degenerated caseous masses, with giant-cells visible at their periphery. Most of the remaining gland-cells showed cloudy swelling and irregular staining, so that the residual ratio of functionating adrenal tissue must have been very small.

TERMINAL HYPOADRENIA

Definition.—A form of adrenal insufficiency occurring late in the course of an acute febrile disease as a result of exhausting functional overactivity.

Symptomatology and Etiology.—The usual type of terminal hypoadrenia is that in which, toward the close of a severe attack of some acute disorder, such as typhoid fever or pneumonia, symptoms similar to those already mentioned under Functional Hypoadrenia appear, *viz.*, extreme adynamia and low blood-pressure, a relative or actual hypothermia, a weak and rapid pulse, a tendency to vertigo and syncope, Sergent's white line phenomenon, nausea and vomiting, and diarrhea. In a general way, the manifestations may be said to be more severe than those of simple functional hypoadrenia, and in some instances the condition is probably a factor in the fatal issue of the case, where such a termination occurs. A so-called "fulminating" or "malignant" course in acute infections is sometimes to be accounted for, it would appear, on the basis of a sudden, marked adrenal insufficiency. Granting that, as Sajous, Sr., has concluded from evidence which he collected, the adrenals are a factor in the protection of the system against intoxications and bacterial invasions, prolonged over-function of these organs in the presence of infectious disease is apt to result in their exhaustion, with corresponding symptomatic manifestations as above enumerated. Comessatti[72] found that in diseases of long duration the adrenin content of the adrenals is much less than in the case of subjects whose death has taken place suddenly; his findings are in harmony with the conclusions more recently reached by Sampaio, previously quoted. Not improbably, in some instances of hypoadrenia in infectious diseases, a vicious circle becomes established, whereby the function of the adrenals, primarily overburdened through excessive demand or the direct toxic action of the germ present, becomes so reduced, from the standpoint of protection against the infection, that the latter develops further; or septic disturbances set in, with consequent additional stress or toxic effect on the adrenals and accentuated adrenal weakness.

Association with other Diseases.—Hypoadrenia of the type under consideration has been observed with special frequency in typhoid fever and diphtheria, but may occur also in a variety of other disorders, such as lobar and bronchopneumonia, scarlet fever, measles, mumps, tonsillitis, erysipelas, tetanus, septicemia, acute peritonitis, bacillary dysentery, Asiatic cholera, typhus fever, and acute nephritis. Goldzieher[73] laid special stress on adrenal insufficiency as a cause of low blood-pressure in septicemia. Nuñez[74] recognizes the following five signs as evidences of adrenal deficiency in typhoid fever: hyposthenia, hypotension, hypocholesteremia, dicrotic pulse, and sphygmothermic dissociation, the pulse-rate being relatively low as compared with the level of temperature. Dumas and Hervier[75] found the two most prominent symptoms of terminal hypoadrenia in acute infections to be a sudden fall of blood-pressure and extreme prostration, the accessory symptoms being hypothermia, vomiting, profuse green diarrhea, and an erythematous rash; definite pathological states in the adrenals were noted by these observers in their fatal cases. Dujarric de la Rivière and Villerval[76] consider adrenal insufficiency a rather frequent complication of amebic dysentery. Naamé[77] deems Asiatic cholera to be, in itself, practically a syndrome of hypoadrenia, and recommends injections of **adrenin** and of **glucose solution** in its treatment. Paisseau and Lemaire[78] observed the acute suprarenal syndrome in some cases of the "algid" type of malaria, the patient, after the febrile paroxysm, becoming motionless from extreme prostration, with cold, cyanotic extremities, and clammy skin, very low blood-pressure, and often vomiting, diarrhea, and colicky pains. Death frequently followed in these cases, while if the patients survived, the condition sometimes passed into chronic or Addisonian hypoadrenia, with skin pigmentation. Portocalis[79] reported four deaths from relapsing fever or malaria with symptoms of acute hypoadrenia of the choleriform and algid types; in each case the adrenals showed old tuberculous lesions, which are thought to have flared up acutely as a result of the intercurrent affection. Sergent[80] called attention to the special predisposition of soldiers, more or less fatigued from active service, to hypoadrenia when they contracted typhoid or paratyphoid fever, choleriform diarrhea, or typhus. Finally, Sanchez Moreno[81] reports a case of what he believes to be a meningeal form of adrenal insufficiency, exhibiting Kernig's sign, anisocoria, vomiting, and headache, with the typical low blood-pressure, tachycardia, uncontrollable vomiting, the white line, and extreme prostration.

Manifestations similar to those occurring in the course of infectious diseases may also result from intoxications of various kinds, traumatism, etc. Thus, Sergent[82] refers to a supposed epidemic of cholera which turned out to have been due instead to severe poisoning from drinking water contaminated by decomposing cadavers. Autopsies in the fatal cases showed marked lesions of the adrenals. Brindeau[83] lays stress on acute hypoadrenia superimposed on chronic adrenal disease as a cause of unaccountable postoperative sudden death. In one case an apparently healthy woman died in the night after perineal repair under chloroform, and the autopsy showed chronic tuberculous disease of both adrenals. In another, a child of eight died on the sixth day after general anesthesia, and each adrenal showed a large hematoma. Many other more or less similar types of cases might be cited.

Diagnosis.—The typical group of symptoms already repeatedly enumerated is that upon which the diagnosis is based. Definite laboratory methods of confirming the existence of adrenal insufficiency have been sought and applied in a few instances. Thus, Sydenstricker, Delatour and Whipple[84] applied Elliott's physiological test and Folin's chemical test in various experimental intoxications in dogs, in anesthesia and chloroform-poisoning, in acute infections, and in pernicious anemia. In some respects his results were at variance with the clinical indications already mentioned. Cooke[85] made a postmortem laboratory diagnosis of adrenal insufficiency in one case by determining the amount of adrenin present in these organs, which were found to be caseous; the adrenin was diminished in both the diseased and the apparently normal portions of the glands.

Treatment.—As in functional hypoadrenia, the chief remedial agent for the terminal hypoadrenia of infections or intoxications is **adrenin or adrenal gland products.** The modes of administration of these remedies have already been presented in part under Functional Hypoadrenia. In pneumonia and typhoid and paratyphoid fever, Mansvetova[86] found 0.5 c.c. (8 minims) of adrenin hypodermatically, repeated every hour or hour and a half, the most efficient procedure for obtaining a sustained improvement in blood-pressure. Sergent,[87] from observations on the treatment of hypoadrenia in typhoid and other infections and in physical exhaustion among soldiers, concluded that, where adrenin alone is used in acute hypoadrenia, larger doses should be given than had previously been employed, *viz.*, at least 2 or 3 mg. (1/32 or 1/20 grain) hypodermatically, in from four to six divided amounts of 0.5 milligram (1/120 grain) each, and also 1 or 2 mg. (1/64 or 1/32 grain) by mouth, to keep up the effects. Moltschanoff,[88] emphasizing the importance of the rôle of the adrenals in diphtheria, urged that adrenin be given early in this disease, before heart weakness becomes manifest. According to Goormaghtigh,[89] adrenin injected daily in the presence of infections not only adds to the blood a substance which is deficient, but also stimulates the adrenals to greater functional activity. Sajous, Sr., states that in cases in which asthenia and low blood-pressure come on gradually, the official dried suprarenals are useful when orally administered in doses of from 0.097 to 0.324 gram (from 1½ to 5 grains) in capsules three times a day. Josué[90] utilizes suprarenal therapy in typhoid fever, for example, for prophylactic purposes; as soon as the pulse grows weak, from 2 to 4 mg. (1/32 to 1/16 grain) of adrenin are given hypodermatically in from four to eight fractional doses. When toxic phenomena are marked, as in diphtheria, adrenin diluted with saline solution is given subcutaneously and an extract of the whole adrenal by mouth. Brindeau[91] states that in cases in which adrenal insufficiency is suspected, operations should be done under local anesthesia, or, if this is impracticable, adrenin should be given both before and after the intervention. Hutinel[92] states that in the hypoadrenia of various diseases, such as scarlet fever, measles, diphtheria, and erysipelas, daily doses of from 0.75 to 1.25 c.c. (12 to 20 minims) of adrenin solution cause the disease to lose any menacing character which it may show as far as cardiac arrest is concerned.

Pituitary extract (both lobes), 0.097 gram (1½ grains) daily, was found useful by Oddo and Achard in cases of typhoid fever exhibiting symptoms of hypoadrenia. Similar effects were noted in diphtheria and erysipelas. In the case of young children, Rohmer[93] has recommended the combined intravenous administration of **pituitrin,** 0.25 c.c. (4 minims), and **adrenin solution,** 0.5 c.c. (8 minims), in treating the hypoadrenia of pneumonia, diphtheria, and typhoid fever.

When heart adynamia has disappeared in patients recovering from hypoadrenia, 0.0324 gram (½ grain) of **dried thyroid,** 0.001 gram (1/64 grain) of strychnin, and 0.065 gram (1 grain) of **Blaud's mass** may be added to the capsules of dried suprarenals already mentioned.

As in functional hypoadrenia, **rest, physical** and **mental,** is an important factor in the promotion of recovery from terminal hypoadrenia

Pathology.—In some instances of terminal hypoadrenia no definite pathological condition of the adrenals is found. In the great majority of cases, however, these organs are at least hyperemic, and frequently they show hemorrhagic or parenchymatous changes. Moschcowitz[94] enumerates the following varieties of adrenal lesions as occurring in association with infections, the first two being the most common: parenchymatous degenerations; hemorrhages; edema of the interstitial connective tissue; infiltration with leukocytes; focal necroses; bacterial emboli, with or without inflammatory reaction; and miliary or larger abscesses. The hypoadrenia may either be induced in previously healthy adrenals as a result of severe infection or intoxication, or occur in chronically diseased, but ordinarily adequate, adrenals under the influence of mild or severe toxic disturbances, exhaustion, etc. According to Reich and Beresnegowski,[95] acute peritonitis takes the lead among infections producing adrenal lesions. In 4 cases of bacillary dysentery developing symptoms of acute hypoadrenia, reported by Remlinger and Dumas,[96] a swollen condition of the adrenals was found at the autopsy in the absence of any other significant finding. Kindley,[97] making a pathological study of the adrenals in 45 fatal cases of acute infectious diseases, found the following lesions: cellular atrophy, 27; congestion, 18; foci of lymphocytic infiltration, 8; small hemorrhages, 2; fibrosis, 2; and cavitation, 4. Cell-atrophy predominated in bronchopneumonia and in typhoid fever, and congestion in lobar pneumonia and cerebrospinal meningitis. Kindley believes his findings to be strong evidence of the importance of adrenal insufficiency in causing low blood-pressure and feeble heart action in acute infections.

ADDISON'S DISEASE (CHRONIC PROGRESSIVE HYPOADRENIA)

Definition.—A disease of the adrenals in which the functions of these organs become, either directly or through their secretory nerves, progressively reduced by organic lesions such as tuberculosis, cancer, fibrosis, etc.

Etiology.—Cases of Addison's disease presenting in complete array all the characteristic symptoms and signs, including melanodermia, are relatively uncommon, but incomplete types of the condition are by no means infrequent. The disease may occur at any age, and may even be congenital. Most cases, however, occur between the ages of fifteen and sixty years.

The typical cause of Addison's disease is tuberculous involvement of the adrenals, either primary, or secondary to tuberculous lesions elsewhere in the body. In some instances, however, a cancerous or other unusual form of lesion is the cause, while in still others the adrenals show no perceptible lesion, and the disturbance of adrenal function appears to be due to disease in, or in the vicinity of, their secretory nerves, whether in the ganglia of the suprarenal plexus, the splanchnic nerve-trunks, or the spinal cord near the point of emergence of the nerve pathways leading to the adrenals. Cases have been reported in which bronzing appeared through prolonged compression of the semilunar ganglia and solar plexus. In the case recorded by Anglade and Paquin there was extensive tuberculosis of the lungs and spinal cord, but no tuberculous lesions in the adrenals. Addison's disease has also been reported as a late sequela of acute infections such as scarlet fever, measles, and tonsillitis. According to Bittorf,[98] atrophy or chronic interstitial inflammation of the adrenals is, after tuberculosis, the most frequent cause of Addison's disease. Other pathologic conditions noted include gumma, sarcoma, cavernous angioma, echinococcus disease, and mycosis fungoides.

PATHOGENESIS.—The usual conception of the pathogenesis of Addison's disease is that of a deficient functional activity of the adrenals (and subsidiary chromaffin lesions), whether the deficiency is due directly to pathological changes in these tissues or is in some manner indirectly produced. This corresponds with the views of Sajous, Sr., who looks upon the hypothermia and dyspnea as due to deficient oxygen intake because of inadequate participation of the adrenal secretion in the respiratory process, the hypotension and weak heart action as due to lack of the tonic action of this secretion on the cardiovascular tissues, the vomiting as due to a similarly produced gastroptosis and insufficient evacuatory peristalsis, and the constipation or diarrhea to intestinal atony or passive congestion of the mucosa. An important clue to the general asthenia and striking lack of motor endurance is afforded by the observation of Mackenzie[99] that in adrenalectomized dogs there is diminution of the power to form glycogen from glucose. This agrees with the findings of Porges,[100] who, upon killing dogs some hours after adrenalectomy, when they were showing pronounced muscular weakness, found the livers and voluntary muscles to have an extremely low glycogen content as compared with the normal amount. The melanodermia of Addison's disease has been ascribed to sympathetic irritation and to changes both in the adrenals and in the nervous network surrounding them (Loeper); according to Sajous, Sr., and Laignel-Lavastine it is due directly to the adrenal lesions. Von Neusser and Wiesel[101] have emphasized a participation of status thymicolymphaticus in the pathogenesis of Addison's disease, while Leonardi[102] considers that it is a general affection of the sympathetic system, with added involvement of the thyroid and pituitary glands.

Symptomatology.—The clinical manifestations of this disorder are in the main those of functional hypoadrenia, but with the addition of certain special features. The chief of these features, aside from the usual chronicity of the disease, is the characteristic pigmentation of the skin, or bronzing, often involving also the mucous membranes. This bronzing is to some degree peculiar to the protracted, gradually progressive forms of adrenal impairment, but is also occasionally noted in the more acute varieties, *viz.*, in the types of cases already described under Functional Hypoadrenia, and especially under Terminal Hypoadrenia. Again, it is not constantly present, even in true Addison's disease, some patients dying before pigmentation has appeared. The parts of the body to become pigmented first are often those exposed to light, and after these the external genitalia, areolæ, axillæ, about or below the umbilicus, and the flexor surfaces of the joints. As a rule, the melanodermia occurs in the form of scattered brownish macules, but these may later become confluent and the whole integument show discoloration. Frequently the mucous membranes become pigmented before the skin. Discoloration of the inner surfaces of the cheeks, labial commissures, and genital mucosæ is especially typical. In the colored race patches of skin darker than elsewhere may be perceptible.

Among the other symptoms, asthenia is a dominant feature. Ergographic studies have shown that the muscular weakness of Addison's disease is particularly characterized by lack of endurance, so that after a few vigorous contractions, fatigue and exhaustion appear with extreme rapidity. Eventually there is constant lassitude, and the patient avoids the slightest exertion, even the ingestion of food becoming a difficult matter for him.

Gastro-intestinal disturbances of various kinds are common in Addison's disease. Anorexia is usually present and constipation is the rule at first, although later diarrhea may be a prominent symptom. Sudden vomiting is an almost constant manifestation, and occurs with increasing frequency as the disease progresses. Emaciation results from the inability to take and digest food properly.

Circulatory weakness is a pronounced feature. Vascular hypotonicity is reflected in a reduction of blood-pressure from the beginning of the disease, and in the advanced stages of the disease a systolic pressure as low as 50 mm. Hg. may be observed. A tendency to syncope from brain ischemia constitutes a secondary effect, and Sergent's "white line" phenomenon is looked upon as a special mode of contractile reaction of the vessels to irritation, in some way related to their low degree of tonicity. The body temperature in Addison's disease in the absence of complications, is typically subnormal, and the patient is easily chilled. This is in harmony with the view of Sajous, Sr., that the disease is essentially one of deficient oxidation and lowered metabolism, these conditions resulting from lack of the adrenal respiratory function in these cases. Dyspnea is also frequently present. In some instances the patient complains of severe abdominal and lumbar pains from the very beginning of the illness. These pains are characteristically of sudden onset.

Other manifestations of advanced Addison's disease comprise a tendency toward impairment of vision and hearing, due to ischemia of the special sense structures, and a toxemia manifested in headache, irritability, muscular twitchings, delirium, and convulsions. Some cases exhibit frequent yawning. The mental condition is, typically, apathetic, with either insomnia or an increased tendency to sleep. Loss of memory, dizziness, tinnitus, muscæ volitantes, and paresthesias are sometimes noted. Frequently the reflexes are impaired.

The course of the disease and the clinical picture are rather variable. Often the syndrome is not completely present. Some cases are apparently acute, the autopsies showing, however, chronic adrenal lesions. In an acute case reported by Lippmann,[103] low blood-pressure, asthenia, toxic manifestations, and pigmentation appeared in rapid succession, with death on the eighteenth day. Such cases merge insensibly into the picture of terminal hypoadrenia, previously considered. Kaplan and Greeff[104] present 3 cases of what they term adrenopathic hyperchlorhydria. Without attempting to offer definite proof that these patients were actually suffering from adrenal impairment (although each did present certain adrenal symptoms), the observers call attention to the striking benefit which they obtained in these cases by the administration of very small amounts of dried suprarenal, such as from 0.0162 to 0.0216 gram (1/4 to 1/3 grain) doses once daily or at longer intervals. Objective proof of the action of the drug was secured by examinations of the gastric contents before and after administration.

Diagnosis.—In cases unaccompanied by skin pigmentation, the diagnosis may be made on the basis of the striking weakness and lack of endurance of the patient in contrast to his relatively well-nourished aspect, together with the low blood-pressure, unaccountable gastro-intestinal disturbances, and, perhaps, pain in the abdomen and back.

Pigmentation is especially diagnostic when pronounced and coupled with asthenia. The latter usually precedes pigmentation, and is therefore likely to be available as a corroborating feature. Of considerable diagnostic import is the fact that the pigmentation of Addison's disease shows a marked preference for mucous membranes. The skin discoloration of progressive anemia is distinguished by its lemon tint, and by repeated blood examinations. Malignancy is distinguished by the more pronounced wasting and usual lack of evidence of the tumor; arsenical intoxication, by the relative absence of oral discoloration, the usual skin hypertrophy, and the history of arsenical medication; vagabondism with phthiriasis by the rough skin and scratch marks; pregnancy is identified by repeated local examinations; malaria, by the history, associated symptoms, and blood examination; hepatic cirrhosis, by the absence of mucous membrane involvement and by the liver symptoms; and bronzed diabetes, by the glycosuria and hepatic enlargement. In melanodermia associated with tuberculosis, it may be very difficult to decide whether or not Addison's disease coexists; extraordinary asthenia would indicate its presence. The preëxistence of tuberculosis suggests Addison's disease where there is marked or progressive loss of strength without emaciation but with more or less pigmentation.

In very mild or incipient Addison's disease the diagnosis may be merely a presumptive one. Striking benefit from adrenal medication, where the usual tonics and stimulants have completely failed is of some diagnostic significance, but should not be too implicitly relied upon.

Treatment.—**Transplantation of adrenal tissue** is doubtless the chief desideratum in the treatment of well-developed Addison's disease with serious adrenal lesions, but as yet few practical results have been obtained in this direction. Attempts at transplantation of adrenal tissue from an animal into a patient with Addison's disease have often ended disastrously, apparently because of the introduction of an excessive amount of tissue, causing a dangerous or fatal reaction in an organism sensitized to the adrenal products through habituation to a relative absence of these products. D. M. Morton,[105] however, transplanted an adrenal from a patient who had died of heart disease into the recti abdominis muscles of a woman of thirty-five with typical Addison's disease. The patient was soon restored to relatively good health, with lessened pigmentation, rise in blood-pressure and a gain in weight of sixteen pounds.

In the absence of a reliable procedure of transplantation, **opotherapy** is in order. This may not only tend to make up for lacking adrenal products, but may also excite hypertrophy of what healthy adrenal tissue remains. Great variation exists in the amount of adrenal product required for beneficial results in different cases. In a case reported by Bate[106] 0.0054 gram (1/12 grain) of adrenal gland caused marked improvement, while in a case recorded by Suckling[107] the amount was increased gradually to 11.34 grams (175 grains) a day. As an initial dose, from 0.065 to 0.195 gram (1 to 3 grains) of **Suprarenalum siccum,** U.S.P., may be given twice daily during meals; or **fresh sheep or ox adrenals** may be administered in doses of from 0.324 to 0.972 gram (5 to 15 grains). The temperature and blood-pressure are of some service as criteria of the proper dosage. If the 1:1000 solution of adrenin is used, 5 minims (0.30 c.c.) may be given three times a day, and then increased, according to the effect. The fact is always to be borne in mind that the more advanced the case, the more sensitive the system is likely to be to adrenal products.

While complete recovery under adrenal opotherapy in a well-established case of Addison's disease is infrequent, marked improvement is nevertheless often produced. Thus, in a case reported by Osborne,[108] with typical symptoms, including deep pigmentation and a blood-pressure of 100 mm. Hg. systolic and 60 mm. diastolic, the discoloration practically disappeared and the blood-pressure was raised to 110 systolic and 80 diastolic under treatment with suprarenal tablets, 0.065 gram (1 grain) each, three times a day. In the case reported by Satterthwaite,[109] of a young lady with various symptoms of adrenal insufficiency, including complete absence of the radial pulse at times, but without pigmentation, 0.130 gram (2 grains) of **dried adrenal gland** had an immediate effect, although **digitalin, strophanthin, glonoin, quinin,** and **strychnin** had **failed.** The blood-pressure rose from 90 to 115 mm.

Attempts are being made to differentiate treatment with adrenal cortex from that with adrenal medulla, but as yet there is little definite knowledge based upon clinical observation on this point. As to the relative values of adrenin and adrenal substance, Josué[110] holds that the former is especially indicated where cardiovascular disturbance is dominant, while the latter seems more active where "manifestations of autointoxication, such as profound asthenia and nervous and digestive disturbances" are marked.

Addition of **pituitary gland** to the adrenal medication may be of service. According to Ramond and François,[111] **combined adrenal and thyroid** treatment is advisable, *e. g.*, 0.5 gram (7.716 grains) of powdered adrenal and 0.1 gram (1.543 grains) of powdered thyroid each morning upon awaking, the thyroid alone being interrupted for ten days after six days of treatment.

In cases of suspected tuberculous origin, the usual **hygienic-dietetic treatment** for tuberculosis should be recommended; **creosote** and **tuberculin** may also be used. In the rare syphilitic cases, **mercury** and **iodids** may prove highly beneficial. In general, **rest**, in or out of bed, according to the stage of the case, is indicated. **Gastric lavage** may be employed in cases of impaired gastric motility, and **bismuth** for diarrhea. **Glucose** has been found useful to reduce the adynamia and lassitude. Not frequently **Blaud's mass** and other tonics seem to be beneficial.

Prognosis.—Recovery from a fully-developed case of Addison's disease is rare. In less pronounced cases, however, constituting transitional forms between simple functional hypoadrenia and progressive hypoadrenia, partial recovery, at least, may occur if time is given for compensation through hypertrophy of the auxiliary chromaffin structures, or if the pathological process which impaired the adrenal functions is one from which eventual restoration is possible. Death from Addison's disease may occur suddenly, with or without exertion, or gradually from exhaustion, diarrhea, vomiting, septic infection, etc.

Hyperadrenia and Adrenal Hemorrhage

Etiology.—Hyperemia of the adrenals is of frequent occurrence, not only in the passive form, as in cardiac or pulmonary disease, but also as an active hyperemia, particularly in infections such as diphtheria, typhoid fever, pneumonia, variola, and erysipelas. Both bacterial toxins, inorganic poisons such as arsenic, mercury, and lead, and certain vegetable drugs, induce a congestion of the adrenals which, in some cases at least, constitutes a sign of functional hyperactivity of these organs, or hyperadrenia. According to Sajous, Sr., this functional hyperactivity is brought about by excitation of the adrenal center, located in the pituitary body. Goormaghtigh[112] has recently reported a study of 70 adrenal glands taken from the bodies of soldiers who died during the course of infectious processes complicating war wounds. The adrenals showed greater macroscopic changes under these conditions than did any other organs in the body, becoming turgid, reddened, and heavy. The cortex, he states, at once discharges its cholesterol into the blood stream, and begins to secrete more. The adrenin-secreting medulla is also stimulated, as shown by its histological appearance. Where the stress is excessive, pathological changes, such as atrophy, may result.

The adrenals, moreover, are very subject to hemorrhage, owing to the fragility of their blood-channels and to their proximity to the aorta. Early in infections, or under other circumstances when the blood-pressure is increased, adrenal hemorrhage is not an infrequent occurrence, high pressure plus vascular fragility plus demand for adrenal function contributing to this result. Thus, hyperadrenia and adrenal hemorrhage are closely related conditions, the former being an immediate precursor of the latter.

As already pointed out, toxemia and raised blood-pressure are factors in hyperadrenia and adrenal hemorrhage. Arteriosclerosis is a predisposing cause. Pronounced physical exertion, epileptic attacks, and acute nephritis have been observed as exciting factors in adults. Lesné and François[113] have reported cases following erysipelas and other infections in newborn infants. Other authors have reported the condition in a variety of infectious processes. It is very common among young infants, and occasional in adults.

Symptomatology.—In children, and especially in infants, in whom the disorder is common, death may occur from adrenal hemorrhage without previous symptoms, except, perhaps, a purpuric rash and high temperature. More frequently, however, the preceding stage, that of hyperadrenia and adrenal congestion, is marked by such symptoms as vomiting, diarrhea, melena, hematemesis, acute abdominal pain, icterus, and fever. At the time the hemorrhage occurs there is more or less sudden collapse, with cyanosis and hypothermia. Arnaud[114] found, among 80 cases of adrenal hemorrhage, that more than half remained latent, *i. e.*, without apparent systemic effect. In 15 cases, however, there was sudden death within three days; in 8, symptoms of hypoadrenia appeared, in 6, peritoneal symptoms, and in 5, a palpable hematoma. In older children, similar manifestations, followed by death in from a few to forty-eight hours after adrenal hemorrhage, may occur in the various exanthemata, or be due to diphtheria, sepsis, bronchopneumonia, ptomain-poisoning, extensive burns, or severe traumatism.

In adults, there may likewise be sudden death, which may or may not be preceded by marked asthenia. More often, however, a period of acute symptoms simulating an intense acute infection or intoxication is noted, exhibiting, *e. g.*, severe epigastric pain radiating to the back, obstinate vomiting and diarrhea, followed, in turn, by indications of loss of adrenal function, *viz.*, prostration, pronounced weakness of the pulse and reduction of blood-pressure, low temperature, cold sweats, collapse, and death. The skin may exhibit a yellowish discoloration or even an actual bronzing. In the so-called "nervous type" of this disorder, convulsions, delirium, coma, or a typhoid state may be observed. Death, where not immediate, often occurs within from six to twenty-four hours after the hemorrhage.

Diagnosis.—The chief conditions which may require differentiation are intestinal obstruction, appendicitis, cholera morbus, cerebral apoplexy, and arsenical and other forms of poisoning. After the hemorrhage the diagnosis should not, as a rule, be difficult, provided the possibility of adrenal apoplexy is always kept in mind. According to Lavenson,[115] acute hemorrhagic pancreatitis is differentiated by less profound shock and less acute lumbar tenderness but more severe epigastric pain and vomiting.

Treatment.—Actual adrenal apoplexy being almost inevitably fatal, treatment is mainly prophylactic, the object being to prevent or overcome such a rise of blood-pressure, coupled with intoxication in some form, as might rupture the adrenal vessels, especially if a cause predisposing to this accident exists. Administration of normal saline solution by rectum, subcutaneously, or intravenously, according to the urgency of the case, will tend to reduce any existing toxemia liable to raise the blood-pressure, by washing out toxic materials through the kidneys. Actively hypotensive remedies, such as **nitroglycerin, Veratrum viride,** or **chloral hydrate** may also be used. Where, as in some cases, adrenal apoplexy does not cause prompt death, and the patient begins to exhibit manifestations of adrenal insufficiency, the treatment for emergency cases of terminal hypoadrenia, previously described, should be instituted. If the tissue destruction resulting from the hemorrhage has not been too widespread, the likelihood of recovery may be enhanced by the administration of **adrenal** or **hypophysis preparations.**

Pathology.—Owing to active congestion plus high blood-pressure, or to passive congestion from pressure of any origin upon the adrenal veins, the adrenal capillaries yield, interstitial hemorrhage resulting. At times the whole parenchyma is destroyed and the organ dilated, or complete rupture may occur and the blood enter the peritoneal cavity. Small ecchymoses into the adrenals occur frequently in various infections. Tuberculous changes in these organs predispose to rupture when any additional stress is imposed. Rupture in infants has been ascribed to compression of the inferior vena cava during labor, and to litigation or prolapse of the funis, as well as to a rise in blood-pressure due to infection or intoxication.

Hematoma of the Adrenals

Where, in the course of an infection or intoxication, acute hyperadrenia occurs and is followed by hemorrhagic extravasations in the adrenals, there may gradually develop at the site of the hemorrhage what has been termed an "adrenal hemorrhagic pseudocyst" or adrenal hematoma. By reason of the gradual destruction of adrenal tissue, the cyst contains not only blood, but also cellular débris, cholesterin crystals, etc., shreds or residua of the cortex of the adrenal lining its walls.

Etiology.—Small blood-cysts formed in the adrenals in such diseases as diphtheria, typhoid fever, osteomyelitis, hepatic abscess, burns, and tuberculosis appear to be the starting-point of the condition in most instances. Atheroma of the adrenal arteries may be a predisposing factor. Traumatism and thrombosis of the adrenal veins are occasionally exciting factors.

Symptomatology.—The initial symptom is likely to be a local sensation of weight, followed by pain in the loin, which increases in severity and may radiate toward the hip or in other directions. Exacerbations and vomiting may occur after meals. A globular, or oval, smooth, and tense, but elastic mass may be palpable. For a considerable time, even for years, the patient may remain in apparently good health. Then he may suddenly begin to fail and lose weight, and develop dyspnea, thoracic oppression, and sometimes polyuria, hematuria, or even slight bronzing. In other instances, the "cyst" ruptures into the peritoneal cavity, acute peritonitis resulting.

Diagnosis.—Palpation and percussion will usually reveal the mass. Acute pancreatitis is distinguished by its very severe symptoms; pancreatic cyst, by evidences of imperfect fat and protein digestion; hepatic hydatid cyst, by bile-pigments in the urine, cysts in the stools and vomitus, and obstructive manifestations; splenic cancer, by the more nodular growth and the cachexia; and renal cyst, by its usually greater mobility.

Treatment.—**Removal** of the **involved organ** through a lumbar or anterior abdominal **incision** is the approved method of treatment. Kuttner,[116] who successfully removed a large cyst after tapping, found 11 cases in the literature, with 5 recoveries. Occasionally removal of the corresponding kidney has been necessary, owing to intimate adhesion of the mass to this organ. The remaining adrenal suffices to carry on the adrenal functions.

Pathology.—The walls of the cyst range from 1/16 to ⅛ inch in thickness and eventually contain more or less fibrous tissue. The cyst, which in some instances becomes very large, contains broken down blood- and tissue-cells, flakes of fibrin, etc. Semi-organized clots and chalky deposits may be noted.

HYPERNEPHROMA

Occasionally in the adrenal body, but more frequently in the kidney, a form of tumor develops composed of tissue similar to the adrenal cortex and formed from residual bits of adrenal tissue, or "adrenal rests." According to Trotter[117] these growths constitute not less than 75 per cent. of all renal tumors in adults; in children, however, practically all renal tumors are sarcomata. In a few instances, hypernephroma occurs in the uterus, ovary, broad ligament, etc., developing from adrenal rests situated there.

Symptomatology.—HYPERNEPHROMA OF THE ADRENAL.—This tumor usually begins its growth between the first and eighth years, although it is sometimes met with in adults. It exerts a peculiar constitutional effect by virtue of which the child may seem, both in size and mental development, to be two or three times its actual age. Hair grows abundantly over the face, genitalia and pubis; appetite and thirst are excessive; there is a tendency to obesity, and the skin may be dark-hued. The child shows great muscular strength, and the voice is often deep and rough. Precocious sexuality is a typical manifestation. The body temperature is frequently above normal. This condition, generally met with in girls, progresses slowly. In the course of years, however, malignancy of the growth becomes manifest and metastasis and pressure phenomena appear.

HYPERNEPHROMA OF THE KIDNEY.—In this condition, which is far commoner than the preceding, hematuria is frequently the initial symptom. Often the hemorrhages are copious, but weeks or even months may pass between them. A palpable tumor, generally elicited only after a more or less prolonged interval has elapsed since the beginning of hematuria, is located in the loin, often on the right side. In some cases a dull lumbar pain, suggesting lumbago, is the initial symptom; later, it may radiate to the abdomen and testicles. Sometimes this pain comes on suddenly, and is followed by hematuria and frequent urination. As the tumor process progresses, metastasis occurs, typically in the vertebræ, ribs and other long bones, scapula, skull, etc., or in the lungs. Occasionally a metastasis is the first sign of the disease, as in a case reported by Scudder,[118] in which a metastasis in the upper part of the humerus first drew attention to the disease.

Sexual precocity is observed in some cases of renal hypernephroma occurring in the young. In the usual adult case, there may be premature arteriosclerosis and high blood-pressure. The skin is yellowish, swarthy, or smoky, and later pale, as a fatal termination approaches. The total duration of the disease ranges from fifteen weeks to eight years. The final manifestations are secondary anemia, edema of the lower extremities, delirium, and coma.

Diagnosis.—The main diagnostic features are hematuria, frequent urination, lumbar tumor, fragments of tumor in clots passed with the urine (Gelle), high blood-pressure, and fever preceding cachexia. The condition is differentiated from renal calculus by the fact that the pain associated with it keeps up after hematuria. Vermicular and cylindrical blood-clots are suggestive. Cystoscopy and *x*-rays may also be of service. An enlarged spleen is generally nearer the surface and more movable on inspiration.

Treatment.—**Exploratory incision** is considered warranted in the combined presence of hematuria and a growth in the abdomen or in the region of the kidney. According to some, indeed, unaccountable hemorrhage into the bladder is alone a sufficient indication for exploration; unilateral discomfort or tension may suggest the proper side to be incised. The tumor is generally situated in the upper pole of the kidney, just under the adrenal; it may show merely as an enlargement of the organ at this point, or at the hilum. Its removal may be effected extraperitoneally through a lumbar incision. Consentaneous **removal of the fatty capsule** is advised. Every effort should be made to excise the neoplasm completely. A considerable proportion of the cases remain free from symptoms one year after the operation; in later years, however, there is marked danger of recurrence in metastases. Hence the urgency of early diagnosis and excision in this condition.

Pathology.—Hypernephroma, when extensive, often exhibits both cortical and medullary adrenal tissue, and the renal tumors tend to become lobulated through the influence of fibrous bands from the capsule of the kidney. The connective tissue stroma is scanty, while the parenchyma itself consists of polygonal or columnar endothelial cells containing numerous fat vacuoles. According to Gelle[119] transition forms occur between small benign neoplasms, constituting pure aberrant adrenal germs, and large growths with cancerous characteristics.

TUMORS OF THE ADRENALS

A. Malignant Tumors

Sarcoma is the commonest variety of malignant growth of the adrenals in infancy, childhood, and adolescence, and carcinoma most common among adults. Less frequent growths in these organs are malignant hypernephroma, already described, and the group of tumors designated as hemorrhagic adenomata by Prudden. Carcinoma may follow hypernephroma.

Symptomatology.—The usual course of events exhibits merely a period of progressive emaciation and weakness followed by the detection of a tumor posteriorly below the costal margin close to the spinal column. Eventually fixed and immovable, this mass may at first be observed to follow the respiratory movements and to recede under pressure. In infants the abdomen may simply show a gradual enlargement with progressive extension of the line of dullness.

During the period of development of the growth there may be noted: diminishing circulatory power, anorexia, nausea and vomiting, flatulence, and diarrhea, anemia and respiratory manifestations such as cough, râles, localized dullness, hemoptysis, and dyspnea. Skin pigmentation ranging from slight yellowness to actual bronzing occurs in over one-half of the cases. Pain may be felt in the region of the tumor, or extend upward or across the back, to the shoulders. Special diagnostic indications, according to Israel,[120] are: (1) paroxysms of pain and paresthesias in the absence of a palpable tumor, and (2) a febrile course, noted in 57 per cent. of his cases.

In long-standing cases, pressure on the vena cava is likely to result in ascites or edema of the lower extremities.

Metastasis in cases of sarcoma occurs chiefly in the liver and kidney; in the cancer cases it is more frequent, and is commonest in the liver and lungs. Sudden death, with few preceding symptoms, is not uncommon in infants; in adults, as a rule, there is increasing asthenia, unconsciousness, labored breathing, and coma.

Diagnosis.—In cancer of the liver the surface of the organ is lobulated instead of smooth as in adrenal cancer. In cancer or hypernephroma of the kidney hematuria is usually present as a differentiating sign; pain occurs later, and fever is rare. In abdominal aneurysm there is an aneurysmal bruit, and the various signs of adrenal tumor are absent. Hydatid disease affords the hydatid thrill and other suggestive indications.

Treatment.—The obvious procedure is operative removal, although, as a rule, its ultimate results are unfavorable, metastasis having usually occurred before such treatment is applied. **Early operation** alone affords chances of recovery. In unilateral disease serious adrenal insufficiency following the removal of only one of the organs need not be feared, the opposite adrenal being adequate for all ordinary demands on the adrenal functions. If symptoms of hypoadrenia should actually occur, the treatment appropriate for this condition may be applied.

B. Benign Tumors

The commonest benign tumors of the adrenals are adenoma, lipoma, fibroma, angioma, and echinococcus cyst. The paragangliomas or chromaffin tumors, encountered in the medulla of the adrenals or the carotid glands, are borderline growths, neither benign nor highly malignant.

Symptomatology.—Apart from the possible recognition of a tumor mass in the lumbar region, evidences of a special influence of benign adrenal growths on the sex characteristics are sometimes observed. The condition produced, especially in female subjects, has been termed by Tuffier[121] "adrenal virilism," and is characterized by the development of such peculiarities as a masculine face and voice, a thick black beard and mustache, great muscular power and a predilection for hard manual tasks, enlargement of the clitoris, etc. In a case recorded by Michon,[122] in which during life a tumor in the left hypochondrium and a pronounced excess of urea excretion had been the sole manifestations, a large adenoma of the left adrenal was found at autopsy.

Diagnosis.—A tumor in the hypochondrium, in combination with one or more of the special features just referred to, constitutes the basis of diagnostic differentiation.

Treatment.—Measures to counteract hypoadrenia are indicated where this functional disturbance occurs as a result of bilateral adrenal tumor growth. Where pressure symptoms appear, **surgical excision** is required.

DISEASES OF THE THYMUS

General Anatomy and Physiology.—The fully developed thymus, as it is found at puberty, consists of two adjoining lateral lobes, and extends from the level of the fourth costal cartilage up to the lower margin of the thyroid gland in the neck. It lies beneath the sternum and the muscles attached to the latter; its lower extremity is in contact with the pericardium. A fascial layer separates it from the arch of the aorta and the other great vessels. Above, *i.e.*, in the neck, its posterior surface rests against and on both sides of the trachea.

The various lobules of the organ are made up, in turn, of numerous follicles measuring from 1 to 2 mm. in diameter and comprising two portions, cortical and medullary. Each of these contains numerous lymphoid cells, but in the medulla the supporting reticulum of branched cells is coarser than in the cortex, and this portion likewise contains the special nest-like bodies known as the concentric corpuscles of Hassall.

The arteries to the thymus are branches of the superior and inferior thyroid arteries and of the internal mammary artery. The veins leaving it terminate in the thyroid veins and in the left innominate vein. The nerve-supply comprises small branches from the sympathetic system and from the vagi.

While it was formerly believed that the thymus increased in weight from birth only until the end of the second year, Hammar[123] showed, in 1905, that the organ continues to increase until puberty, reaching an average weight of 25 grams at this time. Thereafter it is thought to diminish in size rapidly from fifteen to twenty-five years, at which time it weighs but 5 grams, and then more gradually up to old age, when it may be reduced to less than 1 gram. Even at this period it generally shows remnants of thymic parenchyma, suggesting that its functional activity may persist, at least to some degree, until late in life. Indeed, A. P. Dustin,[124] studying sections of thymus from subjects who had succumbed quickly to traumatism, recently pointed out that at forty years a considerable amount of thymic tissue, rich in the usual small thymus-cells, and hence also in chromatin, may still be found. The organ is, however, extremely sensitive to all influences tending toward cachexia. An infection of a few days' duration, or a few days of underfeeding, free hemorrhage, or repeated minor hemorrhages, suffice to induce immediate retrogression of the thymus. Dustin definitely confirmed this by sections from cases of severe trauma, burns, spinal lesions, hydrocephalus, and cancer. Under these conditions disappearance of the small thymic cells always takes place, not by their actual departure from the thymus, but through cytolysis *in situ,* followed by phagocytosis. Dustin also emphasizes recent researches by Delezenne, showing the thymus to be one of the organs in the body richest in zinc. This zinc, it is held by this author, occurs in intimate association with the nucleolytic ferments.

Regarding the functions of the thymus, many conflicting opinions as well as experimental researches have been recorded. Taking definitely observed facts in the aggregate, it seems rather clear that thymic activity is in some way related to those structures of the body in which compounds rich in phosphorus are of particular importance, *viz.*, the nervous system and the bones. The significance which the thymus might readily have in this direction, judging merely from its own chemical make-up, is illustrated in the statement of Biedl[125] that the amount of nucleinates in the thymus is at least five times as great as that in the lymph-glands. Again, Huiskamp[126] found the most abundant proteid in the thymus to be nucleohiston, a body containing no less than 3.7 per cent. of phosphorus. From these facts it seems at least possible that the thymus constitutes a species of storehouse for phosphorus or phosphorus-containing compounds. Indeed, the conclusion reached by

Sajous, Sr.,[127] as early as 1903, from analytic study of available data, was that "the function of the thymus is to supply, through the agency of its lymphocytes, the excess of phosphorus in organic combination which the body, particularly the osseous, nervous, and genital systems, requires during its development and growth, *i. e.*, during infancy, childhood, and adolescence, or later if need be." Pappenheimer,[128] from a review of various data, has expressed the conclusion that "the constant, and under some conditions, excessive disintegration of nuclear material is the most obvious form of activity which takes place in this organ." Dustin [129] has recently referred to the thymus as playing an important rôle in the regulation of nuclein metabolism, and thinks that Delezenne's nucleolytic ferment occurring in the thymus in association with zinc is probably concerned in the rapid changes to which the thymic cells are liable.

Experimental work to elucidate the functions of the thymus has consisted largely in extirpation and feeding tests. Neither of these can be said to have given conclusive results, although several experimenters have reported rachitic deformities as following thymectomy in early life, together with somnolence, depression, and ultimately even coma and death. Various effects on the thyroid gland and testes have also been described. The value of these experimental observations is in doubt, inasmuch as certain more recent workers have failed to obtain the same results. The fact remains, that what results have been obtained have concerned mainly the bones and nervous system; various clinical observations have at least illustrated a frequent concomitance of thymus disturbance with osseous and nervous disturbance.

There is little evidence that the thymus produces a true internal secretion. Paton and Goodall [130] observed a decrease in the number of leukocytes circulating in the blood after thymectomy, and E. R. Hoskins [131] advances the view that the thymus functions as a lymphoid organ in infancy and childhood, when large numbers of lymphoid cells and leukocytes are required to combat infections. Sajous, Sr., holds, as already pointed out, that the thymus serves, through its lymphocytes, as a source of supply of excess phosphorus in organic combination whenever it is needed. The large content of phosphorus in the organ, as well as a number of other facts and observations, support this view.

Thymus Insufficiency (Hypothymia)

Little is as yet known concerning the effects of thymus insufficiency, although in certain directions suggestive data may be garnered. The organ is liable to premature involution as a result of infectious processes, acute or chronic starvation, *x*-rays, etc., but direct results of such involution are difficult to find. It would seem a possibility, granting that the thymus serves as a storehouse of phosphorus-containing material, that results from its removal may vary according to the nutritive conditions existing at the time in the individual. Where no unusual demand in the system for such material exists, its removal may have no effect at all; the negative results of certain experimenters may be thus accounted for. Infection appears to constitute one of the conditions of unusual stress in the presence of which lack of the thymus may make itself unfavorably felt. Various experimenters have recorded an unusual susceptibility to infection after thymectomy. Ver Eecke[132] found frogs less resistant to infection after this operation, and Hart and Nordmann[133] recognize that the thymus plays an active rôle in protection against infection.

Certain clinical and experimental observations would seem to indicate that absence of the thymus may bear some relation to bone defects. Thus, Lanzarini[134] reports the case of a child twenty-six months old with osseous dystrophy who died of bronchitis; at the autopsy the thymus showed premature sclerotic involution, and all the bones were affected with osteoporosis. Ogata,[135] injecting thymotoxic serum into pups from ten to sixty days old, found the thymus to be atrophied and fibrotic, and, in nearly all the animals, the bones were smaller and less dense.

Especial interest attaches to the influence of the thymus in the development of the nervous system, and in the maintenance of its activity. Basch, Klose and Vogt, Morel and others noted marked mental impairment in puppies in the fifth or sixth month after thymectomy. Examining postmortem 408 non-myxedematous idiotic children, Morel[136] found absence of the thymus in 75 per cent. of the series. Müller,[137] in experiments with fatigued frog muscles, found that the injection of a fresh watery extract of thymus into the abdominal cavity caused a temporary disappearance of fatigue. Del Campo[138] repeated the experiments with mammals. He obtained the same results from intravenous thymus injection; he showed that the action is exerted on the nerve and not on the muscle, and called attention to the fact that thymectomy in animals has been observed to cause myasthenia. E. T. Bell,[139] reviewing the literature, reached the conclusion that some abnormality of the thymus is found in nearly half the cases of myasthenia gravis. Haneborg[140] obtained good therapeutic results from thymus tablets in chorea, and thinks that thymus insufficiency may be a factor in this disease. Convulsions in a congenital idiot were also subdued by thymus medication. Ludlum and Corson-White,[141] examining dementia precox patients with x-rays, concluded that there was less calcium in their bones than in those of other patients. Out of 6 dementia precox cases treated with **thymus extract**, 3 showed excellent results and became practically well; the other cases were of old and much demented patients, so that good results could hardly be expected.

Mongolian Idiocy

The relationship of insufficient functioning of the thymus to certain types of low mental development, and in particular to Mongolian idiocy, is emphasized by Sajous, Sr.[142]

Etiology.—The imperfect mental development of Mongolian idiots is possibly related to an insufficiency of nucleins derived from the thymus gland. Parental weakness also seems to have some bearing in this connection, such idiots being not infrequently the offspring of old parents or of parents markedly different in age. In a series of 176 Mongolian idiots, Leeper[143] found that no less than one-half of these children were the last-born in large families. Slanting eyes, narrow palpebral fissures, straight hair, a flattened nose, a yellowish and doughy skin, and low power of resistance to infections, are features common to the Mongolian idiot and also to the Eastern Asiatic races, especially among the lower classes. Sajous, Sr., thinks that in the latter these features may have arisen in a somewhat similar way, *viz.*, by subsistence through many generations on a diet made up largely of overmilled rice, deficient in vitamins, especially phosphorus-containing substances, with a consequent unfavorable reaction on the nervous system.

Symptomatology.—The manifestations of Mongolian idiocy comprise not only the peculiar slant of the eyes, with prominence of the epicanthal folds, but also bone defects suggesting those observed by some investigators after experimental thymectomy. Rickets is often an accompaniment. The long bones, especially in the lower limbs, are abnormally short, and the patient is of short stature for his age. The chest is flat, the hands stubby, the head rounded and small, the nose squatty, and the ears under-developed. The teeth appear late, are irregular, and are very subject to caries.

Mongolian patients readily acquire infections, especially of the respiratory and intestinal tracts. For this reason few live to middle age.

Possible implication of other endocrine organs, especially the thyroid gland, is suggested by the thick, prominent tongue, the dry, rough skin which is sometimes noted, and the subnormal temperature and poor circulation.

The muscles and ligaments are relaxed in many instances.

Treatment.—Prophylactic treatment of Mongolian idiocy may be instituted by giving to the nursing mother a combination of **dried thymus gland**, 0.324 gram (5 grains), **dried thyroid**, 0.065 gram (1 grain), and **dried hypophysis**, 0.0065 gram (1/10 grain), three times a day during meals, together with a **generous varied diet**. Such treatment is indicated where some of the conditions probably underlying or indicating Mongolian idiocy exist, *viz.*, where the parents are old, or of dissimilar ages, or have already had many children; where affliction or strong emotion has been present in the case of the mother; where there is syphilis or alcoholism; and where the baby is unusually quiet, with loose joints, persistent helplessness, or a suggestion of the Mongolian facies.

The established Mongolian condition is readily influenced only when the patient is as yet very young. The organic products already mentioned should be given. For a child five years old the doses referred to in relation to the mother are applicable. The dose of dried thymus may, however, be further increased, up to 0.972 gram (15 grains) a day. Thyroid or pituitary stigmata may also indicate the necessity for larger doses of the corresponding products. **Good food and life in the country** are of service. **Iron** and **syrup of hypophosphites** may accelerate the improvement. **Enlarged tonsils** or **adenoids** should by all means be **removed.** Patient **mental education** will assist in developing the psychic functions, to which added support is afforded by the measures already mentioned.

Pathology.—Percussion and *x*-ray studies tend to show absence or atrophy of the thymus in some cases and hypertrophy of the gland in others. The hypertrophy is perhaps an expression of an attempt at compensation in a partly diseased organ. As for the nervous system, no organic abnormalities are seen, but merely a deficient development of the brain both as to cellular make-up and as to general size. Evidences of imperfect nutrition of the bones are also observed.

The Thymus in Backward Children

Etiology.—According to Sajous, Sr., the endocrine organs, including the thymus, are in a considerable number of cases at least partially concerned in the causation of slight mental deficiency—degrees of deficiency short of actual idiocy. Where a tendency to myxedema exists, the thymus is frequently defective in addition to the insufficiency of thyroid function, and the mental state is of a sluggish order, replies to questions being given only slowly and with hesitation. In these cases, moreover, the bones not infrequently exhibit rachitic characteristics, and the loosening of the ligaments mentioned above under Mongolian Idiocy.

Apart from endocrine disturbances, hindering influences relative to the environment and diet may also be operative in reducing the mental development in these cases. Tuberculous processes, congenital syphilis, and anemia may also be unfavorable factors. *Prejudicial influences* such as enlarged tonsils or adenoids, errors of refraction, absence of the mental stimulus resulting from association with other children, neglect on the part of the parents of any attempt to enhance the child's understanding and enlarge his vocabulary, etc., must likewise be *remedied* before satisfactory results from organotherapy may be expected.

Treatment.—Stigmata of deficiency of the thyroid, pituitary, adrenal, or thymus glands should be carefully sought and **organotherapy** prescribed in accordance with the findings. Where the hypothymic stigmata of mental torpor, bony deformities, etc., are noted, 0.324 gram (5 grains) of **dried thymus gland,** gradually increased to 0.65 gram (10 grains), together with 0.0324 gram (½ grain) of **dried thyroids,** should be taken in the course of each treatment. This treatment is generally attended by distinct benefit. **Calcium lactate,** 0.13 gram (2 grains), should also be given after each meal. The mental condition and general health may improve consentaneously as a result of this treatment; sometimes, however, the general health alone is influenced. The prognosis, however, should be guarded.

In **training the mind** of the backward child care should be taken not to render him discouraged, unwilling, irritable, and later criminally inclined, by driving his brain beyond its natural working powers. In the special classes for backward children, the extent of backwardness in the individual child should be carefully estimated by the Binet-Simon test or one of its modifications, and the various children should be properly grouped to permit of imparting more or less precisely the amount of instruction suitable for each. Under such a carefully adjusted plan of mental treatment, surprisingly rapid mental advancement is frequently obtained.

Thymus Hypertrophy

Enlargement of the thymus may occur independently or in conjunction with such conditions as status lymphaticus, tonsillar and adenoid hyperplasia, exophthalmic goiter or myxedema, acromegaly, Addison's disease, removal of both testes, epilepsy, myasthenia gravis, congenital syphilis, leukemia, Hodgkin's disease, thymus neoplasm, or the acute infections. A relative enlargement of the organ may be present at any given age, owing to retardation of involution to the size of the organ generally present at that age.

Etiology and Pathogenesis.—The functional effects of thymus hyperplasia, in the sense of an excess of internal secretion or of toxic effects from an over-amount of material rich in phosphorus, are not plainly apparent, although some writers have maintained that in certain cases of exophthalmic goiter excessive thymus functioning is in part responsible for the symptoms of this disease. For the present at least, the main clinical interest of the thymus enlargement lies in its relationship to status thymicolymphaticus, thymic asthma, and thymus death.

The precise relationship of the thymus to the dyspnea and other symptoms met with in these conditions is not as yet completely known, many observers claiming that the disturbances are not due solely or even partially to pressure of an enlarged thymus on the trachea, but arise also by an indirect process, variously described by different writers.

Nearly all instances of thymus disturbances occur among children, especially young children, and in the newborn many instances have been met with. Taguchi[144] has, however, emphasized the fact that some cases do occur in adults, and reports 1 case in a woman of twenty-three and another in a man of fifty-seven.

In some cases what appeared to be conclusive pathologic evidence of fatal pressure on the trachea by the enlarged thymus has been noted postmortem. Stress has been laid by some writers on a supposed susceptibility of the organ to rapid congestion, owing to a relative predominance of its arterial supply over its venous channels; such a congestion, or an edema, might occur, it has been stated, and disappear after death, thus accounting for the fatal results where no enlargement can be found at autopsy. The negative findings, in many instances of thymic death, have led to the proposal of a variety of theories of this accident, *e.g.*, hyperfunction of the thymus (Nordmann, Wooley), excess of "hormone X" and insufficiency of adrenin (Tracy), pluriglandular syndrome resulting in imperfect general development and abnormal susceptibility to trauma (Noel Paton), anaphylaxis (McNeil; Symmers), neurosis, perhaps toxic, and sudden cardiac arrest (Griffith), etc. Apart from direct pressure by the thymus on the trachea, Gismondi [145] calls attention to a vicious circle arising through pressure on the veins from the brain and arm, thus indirectly obstructing the veins in the thymus and causing further enlargement of this organ; at the same time, the bronchial mucosa is congested, and pressure on the pulmonary veins interferes with the aëration of the blood, thus favoring an asphyxial state.

Of late much stress has been laid on the researches of Hammar [146] who, carefully comparing the thymus in 16 infants who had died suddenly from internal causes with that in 16 healthy infants who had died as a result of accident or of other external causes, found the organ alike in the two series, and practically claims that "thymic death" is not really of thymic origin. Among 13 children from nine days to sixteen years old, who succumbed to this condition, only 2 had an enlarged thymus. Symmers,[147] however, studying 249 cases of status lymphaticus examined postmortem, found the thymus hyperplastic in 118 instances.

Symptomatology.—Evidences of thymus enlargement may come on either suddenly or gradually, and, in appearance at least, suggest a narrowing of the tracheal lumen. The predominant manifestation is almost always dyspnea, which may be constant or paroxysmal, and is generally aggravated if the child cries, exerts itself, develops a fit of anger, throws its head back rapidly, or acquires an acute infection, especially diphtheria. Dyspnea is likewise more pronounced during sleep, on account of the dorsal decubitus. Stridor during inspiration is a typical accompanying symptom, as is also inspiratory retraction of the supra- and infrasternal surfaces. Hoarseness and other voice abnormalities are not usual in uncomplicated cases; they have been ascribed, where present, to pressure on the trachea or the recurrent laryngeal nerve. In nearly all instances, cough is an important symptom.

In a more pronounced form of the same affection, the condition is what has been termed "thymic asthma." Suddenly, or following stridor, paroxysms of more severe dyspnea occur, the skin becomes actually cyanotic and later pale, the pupils are dilated, the hands clenched, and the general appearance suggests imminent suffocation. Death may, indeed, occur; but in many instances the attack soon passes off, either completely or leaving a residual stridor.

Where death takes place suddenly without a history of previous difficulty in breathing the term "thymic death" is applied. Such deaths are often brought about by factors which would be of little or no consequence in a normal individual, *e.g.*, trivial surgical operations, anesthesia, fright or other emotion, bathing, or the presence of some acute infection.

It is claimed that pressure on pulmonary vessels, in connection with thymus enlargement, may induce pronounced congestion of the bronchial vascular distribution, and may eventually lead to capillary bronchitis and bronchopneumonia. Dysphagia, more or less marked, is another possible result of thymus hypertrophy.

In addition to the symptoms especially related to the thymus, a general enlargement of the lymphatic structures may be noted, together with a pasty skin and adiposity. Frequently there are associated changes in the chromaffin system in these cases, to which the term "status thymicolymphaticus" is specifically applied. Thymus death is held to be particularly common among such patients.

Diagnosis.— In occasional instances a prominence above the manubrium sterni, either continuous or when the head is thrown backward, bulging of the manubrium, or a tumor rising in the jugular fossa in inspiration or in crying, occurs as direct evidences of thymic enlargement. More frequently, the enlarged organ can be mapped out by gentle percussion. Thymus dullness is triangular, with its base at the level of the sternoclavicular joints and its blunt apex directed downward, above or opposite the third ribs. The thymus is considered to be enlarged when the dullness extends more than one centimeter beyond the margin of the sternum on either side. Generally its greatest extension is toward the left. Benjamin and Lange[148] recommend the "threshold method" of percussion for the thymus. The child having been placed on its back on the mother's lap, percussion is commenced well outside the thymic area, with strokes so light that only the faintest possible personance is heard with the ear within a few inches of the site of percussion. Dullness begins where the resonance becomes completely inaudible, as confirmed by the *x*-rays.

The most certain method of diagnosis of thymus hypertrophy is by radiography. The normal thymic and cardiac shadow is flask-shaped, with the narrow neck of the flask, which corresponds to the thymus, extending from the first or second dorsal vertebra to the fifth or sixth. While gradually becoming broader below, the normal thymic shadow shows concave lateral margins. The shadow of the enlarged thymus, on the other hand, becomes confluent below with the heart shadow by convex lines instead of by concave. An enlarged thymus may thus sometimes be detected in an apparently normal child; it may give no trouble until added stress is placed on the heart or respiration, or until an acute infection is acquired.

Enlarged bronchial glands afford a higher and less superficial dullness than thymus enlargement (Boggs). Stridor due to pressure by tuberculous lymph-glands may be differentiated by the fact that it disappears during sleep, lessens when the child is inclined forward, accompanies expiration only, and seldom occurs before the fourth month;

it usually develops only a few days before death. Bronchial lymphatic disease is generally the cause of stridor appearing after bronchopneumonia or pertussis.

Hyperplasia of the lymphatic tissues at the root of the tongue has been stressed by some observers as an indication of enlarged thymus.

Treatment.—PROPHYLAXIS.—The prophylaxis of attacks of thymic asthma in children subject to it consists, in the first place, in the **avoidance of all causes of excitement** and of fits of crying or screaming. The child should not be permitted to throw his head far backward, nor to run or jump. **Very hot or cold baths,** as well as swimming or bathing in fresh or sea-water, should be **avoided.** The child should spend his time quietly out of doors, preferably in an even climate. Correct **hygienic conditions,** and a **wholesome diet,** should be insisted upon. Adenoids, enlarged tonsils, nasal catarrh, syphilis, or rickets, if present, should each receive proper treatment, and the child should be safeguarded as much as possible from exposure to acute infections.

Spontaneous recovery from thymic asthma occurs not infrequently. Painting the skin with **iodin** has proved of value in Gismondi's experience,[149] in promoting retrogression of thymic enlargement in young infants.

GENERAL TREATMENT.—For the relief of actual attacks of thymic asthma, palliative measures consist in the **application of heat or cold** over the thymic area, **purgation,** and the administration of **heart stimulants** and of **oxygen gas** when indicated. Where palliation fails to bring relief, ominous hindrance of respiration being present, **intubation** through the larynx or a tracheotomy opening, with a tube sufficiently long to attain the bifurcation of the trachea and overcome any existing pressure effect at this point, has been recommended.

ROENTGENOTHERAPY.—Reduction of thymus tissue with the **x-rays** has found favor of late. Friedlander[150] noted improvement under the rays within from twenty-four to forty-eight hours in the average case, and emphasizes the necessity of a sufficient *x*-ray dosage, repetition of small doses at unduly long intervals having been followed by death in several very urgent cases. Benjamin and Lange,[151] describing their procedure in *x*-ray treatment, favor the use of a Coolidge tube and a 9½ inch spark. The rays are filtered through 4 millimeters of aluminum and a piece of thick leather. The target skin distance is about nine inches. A single dose of 25 milliampère-minutes over the anterior surface of the chest proves sufficient in mild cases, but in more urgent cases such a dose is given both anteriorly and posteriorly at the first treatment, and the procedure repeated in a day or two. If there is no urgency but the case is well marked, three treatments are usually given, at weekly intervals. P. H. Cook[152] refers to cases in which symptomatic relief occurred within three and a half hours after the use of the *x*-rays.

According to Friedlander and others, a thymus gland partially involuted by the *x*-rays is capable of regeneration. Lange recommends that recurrences due to such regeneration be kept under observation and given further treatment.

MEDICINAL TREATMENT.—**Adrenin** in small doses, administered daily, is stated by Franchetti and Pende to have been of service in thymic hypertrophy. Pende prefers its use combined with pituitary extract to its administration alone. **Dried thymus gland** apparently has **no effect** upon the enlarged thymus.

SURGICAL TREATMENT.—Surgical treatment of the condition has given good results in a number of instances. The earlier operations of **exothymopexy** and **resection** of the upper portion of the sternum have been largely **abandoned,** and the procedure usually carried out is a **partial thymectomy.** A number of observers recommend this operation where dyspnea is urgent but not sufficiently threatening as to require immediate intubation. Among them is Cotti,[153] who reports several cases in which the patient thus regained perfect health, after being subject to alarming choking spells. C. A. Parker,[154] analyzing 50 published cases of thymectomy up to 1913, performed at all ages, noted 17 deaths, but recommends the procedure because of his favorable personal experience with it.

In performing thymectomy, a transverse incision is made above the manubrium sterni, and the fascia and muscles are divided or separated in the midline. The thymus, thus exposed, is then pulled gently upward and resected. Crotti recommends an extracapsular resection where, as is usually the case, the organ is easily liberated. Where there has been a perithymitis, however, the capsule of the organ is opened and the parenchyma carefully shelled out. The precaution should be taken of clamping all loose connective tissue attached to the thymus. The last essential step in the operation consists in ligating the organ rather tightly at its base and then cutting it at a safe distance from the ligation. In most cases general anesthesia may be employed for the operation, but in the newborn, or where dyspnea is extreme, local anesthesia or no anesthesia at all may be advisable. The fact should be remembered in this connection that in status lymphaticus with enlarged thymus, death during general narcosis has been a relatively frequent occurrence.

Pathology.—Enlargement of the thymus is at times due merely to deposition of an unusual amount of fat. Where the gland tissue is actually hyperplastic, the hyperplasia may be either general—a form probably found, according to Dock,[155] only in infants—or, as is frequently the case, confined to the thymic medulla, while the cortex may, instead, be hypoplastic. Generally the main mass of the thymus is located behind the upper portion of the sternum. Lower prolongations may extend downward as far as the apex of the heart, and upward prolongations for a considerable distance up the neck. These extensions may be very tortuous. The whole organ is paler than normal, and it is usually softer in consistency.

In status thymicolymphaticus one finds, also, such conditions as enlargement of the cervical, axillary, and mesenteric lymphatics, and of the tonsils and spleen; a small heart, a narrow aorta, a large brain, thyroid degeneration, and a small vagina and infantile uterus may be noted.

DISEASES OF THE PINEAL GLAND

General Anatomy and Physiology.—The pineal body is situated beneath the splenium of the corpus callosum and is attached anteriorly to the habenular commissure and the posterior commissure above the opening into the aqueduct of Sylvius. Its cells contain large nuclei with highly granular periphery, and are arranged in irregular lobules or follicles held in position by a small amount of connective tissue. In mammalian fetuses the organ has been found to be highly vascular, and Jordan[156] observed a few white nerve-fibers, together with a neuroglial reticulum. Ramon y Cajal[157] describes sympathetic fibers in the organ, constituting a plexus in the vicinity of the glandular cells.

Histologically, the pineal body gives evidences of functional activity mainly in early life, being apparently most active, in man, in the seventh year. Thereafter it undergoes involution, the gland parenchyma becoming reduced, and the connective tissue and neuroglia increased. A certain amount of parenchyma has been observed to persist, however, even in old age.

As for the function of the pineal body, little that is convincing has been gleaned from experimental investigations, the results reported by different experimenters being contradictory. Sarteschi, Foa, and Horrax state that pinealectomy in young animals results in precocity of development. According to the last-named author,[158] male guinea pigs subjected to this operation show hastened development of the sexual organs, while females show a tendency to breed earlier. Pellizzi[159] has advanced the view that the function of the pineal body is to exert a moderating influence upon genitosomatic development. On the other hand, Dandy,[160] on removing the pineal body from dogs through the corpus callosum, failed to note effects on the genital or general development, and saw no reason to believe that the organ has any active endocrine function of importance, either in young or adult dogs.

Feeding experiments with pineal substance seem, where physiological effects have actually been noted, to cause changes of the same order as those resulting from pinealectomy. Thus, McCord,[161] feeding young guinea pigs with pineal tissue from other young animals, observed a 40.9 per cent. excess in the rate of growth in a period of eleven weeks. Relatively minute amounts of the product sufficed at times to accelerate growth, although when once the maximum adult size of the animal was attained, no further action took place. The general conclusion reached from a total of 400 experiments in young chickens, dogs, and guinea pigs, was that the agent nearly always caused a more rapid growth of the body than the normal, with an early sexual maturity. Testes from animals given pineal substance were 50 per cent. larger than those from others, and exhibited premature and very active spermatogenesis.

Again, paramecia subjected to the influence of pineal extract divided more frequently, while tadpoles similarly treated grew to double the size of the controls and later showed a markedly precocious transformation into adult frogs. Nevertheless, the results of the aggregate of observers on pineal feeding have been inconclusive. Hoskins,[162] administering various endocrine products to white rats, concluded that neither pineal extract nor thyroid, thymus, or pituitary substance exert any effect upon the rate of development of young rats. McCord and Allen[163] found that pineal administration is capable of controlling pigment-cell changes in tadpoles. When fresh pineal substance was fed to ten-day tadpoles a marked retraction of the pigment-cells took place, so that at the end of thirty minutes the animals were noticeably lighter than the controls, and after forty-five minutes still more translucent; this effect persisted for from three to six hours.

From reported experiments McCord concluded that the pineal gland is an endocrine organ whose functions are, however, of minor significance in the general activity of the endocrinous system. According to Sajous, Sr., the pineal is not a ductless gland, but a neural organ, probably of temporary use during the developmental period.

Tumors of the Pineal Body

In 1907, on the basis of observation of cases of pineal tumor accompanied by certain peculiarities of development, Marburg[164] thought it possible to recognize in pineal dysfunction the cause of a special syndrome. The apparent effects which he noted were both local and general. The local effects comprised the usual manifestations of increased intracranial pressure and neighborhood symptoms due to encroachment on the corpora quadrigemina and cerebellum, *viz.*, oculomotor, pupillary, and ataxic phenomena. The general or metabolic effects apparently due to disturbed pineal function were: early maturity of the sexual organs, with premature pubic and general growth of hair, change of voice, precocious thought and speech, and such a pronounced acceleration of development that a child of five or six years appeared as one eleven or twelve years of age. Bailey and Jelliffe[165] have suggested adiposity, and in some instances cachexia, as probable further manifestations of pineal disturbance.

As a matter of fact, however, effects such as those just mentioned have accompanied pineal tumor only in a small proportion of cases. Practically the whole subject of pineal pathology is still in doubt, and it is by no means certain that the effects ascribed to the pineal body by Marburg and others are actually related to disturbances of its functional activity.

According to Timme,[166] a close relationship exists between pineal disease and progressive muscular dystrophy. In a series of cases of this affection occurring in different generations of the same family, he found, upon careful examination of several of the subjects, including *x*-ray study, definite evidence of disease of the ductless glands, and notably of the pineal body.

McCord thinks that not enough attention has been paid to possible hormonic relationships of the pineal body to other endocrine organs. Uremura[167] has suggested a relationship of the pineal to the anterior lobe of the pituitary body, having noted that in some cases of adiposity the pineal and this lobe are both very large. Again, he reports 3 cases of tumor atrophy of the pineal body in which the anterior lobe of the pituitary was likewise atrophied.

Treatment.—In view of the prevailing uncertainty as to the relationship of the pineal body to any distinct clinical syndrome, nothing definite can be stated as to the indications for pineal administration in tumor or other destructive lesions of this organ. **Removal** of a supposed **pineal tumor** by operation is as yet **impracticable,** the inaccessibility of the organ rendering such an undertaking far more hazardous than in the case of the pituitary body. Palliative treatment for cases of pineal tumor consists in the administration of **analgesic drugs** to relieve the painful manifestations, various suitable measures for tinnitus, cerebellar symptoms, etc., **roborant treatment** calculated to delay cachexia, and **lumbar puncture** for its influence in allaying pressure symptoms when present.

PINEAL INSUFFICIENCY IN BACKWARD CHILDREN

As already pointed out, our knowledge of the clinical effects of pineal overactivity—if, indeed, such a condition may actually occur—is still clouded with doubt. Equally, or even more, uncertain are the results of pineal insufficiency. Dana and Berkeley, coöperating with Goddard and Cornell,[168] were led from observation of the results of pineal feeding in children and animals to conclude, in 1913, that in cases of mental retardation in children pineal substance has the power to greatly stimulate the sluggish mental functions. Unfortunately, later work has failed to confirm this conclusion, and no definite indications for pineal medication in backward mental states are recognized at present.

ENDOCRINIC DISORDERS OF THE OVARIES

General Anatomy and Physiology.—The gross anatomy and anatomical relationships of the ovaries are so well known that they need not be given here. The main feature to be borne in mind for our present purpose is that the ovaries embody not only an externally secreting mechanism, the activity of which results in the extrusion of ova as external secretory products, but also endocrine structures, *viz.,* (1) the interstitial tissue, which consists of epithelioid cells embedded in the stroma of the ovaries either in scattered fashion or in cell-groups forming glandular alveoli; (2) the corpus luteum, which remains after metamorphosis of the collapsed graafian follicle from which an ovum has been extruded.

The so-called "cyclical functions" of the corpus luteum consist, according to Leo Loeb,[169] in retarding ovulation and in sensitizing the uterine mucosa in order that a maternal placenta may be produced upon excitation of this mucosa either by the ovum or by mechanical means. The influence of the corpus luteum in retarding ovulation is shown by the fact that where all the corpora lutea are excised at an early period in the sexual cycle, the next ovulation comes much earlier than would otherwise have been the case.

The "non-cyclical functions" of the endocrine ovarian tissues consist in the maintenance of a favorable nutritive (trophic) condition of the uterus and mammary glands, and in the development and maintenance of the female secondary sexual characteristics of the individual. Gradual atrophy of the uterus and mammæ occurs if the ovaries are removed, or at the menopause, while removal of the ovaries early in life results in loss of the female secondary sexual characteristics and a tendency toward the obtrusion of male characteristics.

Eunuchoid types of individuals, with definite peculiarities of stature, skeletal arrangement, and endocrine gland development, occur where the influence of the ovaries has been eliminated and, in common with the testicles in the opposite sex, the ovaries are believed to be operative as endocrine organs even during infancy and early childhood.

According to the experiments of Loewy and Richter[170] and those of Murlin and H. Bailey,[171] removal of the ovaries in some way reduces metabolism and oxygen consumption. The last-named authors noted a decrease of metabolism of from 6 to 17 per cent. in bitches, after castration, together with a gain in weight from the diminished tissue combustion. A distinct possibility is recognized, however, that these effects of oöphorectomy may be exerted indirectly rather than through the direct influence of an ovarian internal secretion. Indeed, a normal animal showed greater lowering of metabolism after the removal of the ovaries than did one in which thyroidectomy had already been performed. It may, therefore, be suspected that the removal of the ovarian influence actually reduces metabolism through cessation of stimulation of the thyroid gland.

That the ovaries may to some extent control the metabolism of phosphorus and calcium in the body is suggested by certain clinical observations. Thus, in osteomalacia, improvement after bilateral oöphorectomy might be attributed to reduced excretion of these constituents of the osseous tissue.

It is not as yet definitely known whether the endocrine function of the ovaries which results in the development and maintenance of the female secondary sexual characteristics is carried on by the interstitial cells of the ovaries, by the corpus luteum, or by both. In experimental tests with various ovarian preparations, the majority of investigators have found the corpus luteum either inactive or less active than other portions of the ovary. This agrees with the results of the clinical studies of W. P. Graves,[172] who was led to especially emphasize the rôle of the interstitial cells of the ovary as endocrine tissue, and to conclude that preparations of the whole ovary are more effective clinically than extracts of the corpus luteum. He considers that the interstitial ovarian cells correspond to the lutein cells of the theca interna of the atresic follicle or theca lutein cells of the corpus luteum, and recommends that ovarian extracts be prepared so as to include the stroma of the ovaries, in order to take advantage of the atresic follicles present. Extracts made from pregnant animals in the manner just mentioned proved particularly active clinically, while extracts made from the corpora lutea of pregnancy were found to be too toxic to permit of their practical employment.

The nature of the ovarian principle or principles which, directly or indirectly, produce the endocrine effects—including the effects upon the sexual characteristics—exerted by these organs is not as yet known. Various supposed principles or combinations of principles have, indeed, been obtained from the ovaries, but the results of the different investigators in this direction have diverged so widely that no definite conclusion can be said to have been reached. According to Sajous, Sr., who lays stress upon the resemblance of the interstitial cells of the ovary to the cortical cells of the adrenals—a resemblance to which attention had previously been called by Mulon, Wallart and others—the ovarian internal secretion results mainly from the activity of adrenal rests in the corpora lutea as well as in the interstitial organ of the ovaries.

ENDOCRINIC OVARIAN INSUFFICIENCY

The effects of diminution or cessation of ovarian internal secretion after the completion of body growth correspond, in general, to those of the natural menopause. On the other hand, where this ovarian function is, for some reason, eliminated during the developmental period, somewhat different and more striking abnormalities result, which constitute patent evidence of the importance of the ovarian internal secretion at this time.

Etiology.—One of the frequent causes of ovarian endocrine insufficiency is the removal of these organs at operation. They may have been impaired by local disease destructive to the functionating ovarian tissues. According to Bandler,[173] depression of ovarian function may result from a too thorough uterine curettage, such a procedure eliminating the usual stimulating action of the endometrium on the ovaries, and thus causing, in turn, atrophy of the uterus.

Secondary diminution of endocrine ovarian function due to primary impairment of other ductless glands is a frequent occurrence. It may be met with as a result of thyroid disease, whether myxedema or exophthalmic goiter. In involvement of the pituitary body, the adiposogenital syndrome may develop, characterized by progressively increasing obesity coupled with diminished ovarian function and menstruation, and a tendency to atrophy of the uterus and ovaries. Again, in the second stage of acromegaly, likewise due to pituitary disease, the functions of the ovaries and uterus are in abeyance, and menstruation is markedly diminished. In insufficiency of the medulla of the adrenals, as in Addison's disease, secondary hypofunction of the ovaries may be produced, often after a preliminary stage of hyperactivity of these organs. According to Bandler,[174] the amenorrhea of lactation, commonly attributed to inhibition of the corpus luteum by a hormone from the mammary glands, may result, finally, in inhibition of ovarian function as a whole and in atrophy of the uterus; these effects may usually be counteracted by the administration of **ovarian extract, thyroid substance,** and **iron** and **arsenic.**

Symptomatology.—The symptoms of endocrine ovarian insufficiency in adults are commonly considered to include nervous and vasomotor disturbances such as unusual general excitability or nervous sluggishness, sensations of dizziness, flushes, and sweats. Dysmenorrhea with a scanty, irregular flow, or amenorrhea and sterility, appear as the effects of the condition upon the genital tract itself.

Clinically it is noticed, however, that the various nervous and vasomotor symptoms do not occur in complete array in all cases of oöphorectomy. According to Graves,[175] indeed, the majority of patients suffer comparatively little inconvenience, and sometimes none, in consequence of the removal of the ovaries, a circumstance which he ascribes to the assumption by these organs of only a subordinate rôle among the ductless glands, after maturity. Hot flushes are held by this author to be the only specifically characteristic symptom of impaired endocrine ovarian function, although alternate sensations of heat and cold, dizziness, sleeplessness, palpitation, and feelings of anxiety often occur also, in combination with the hot flushes, or even independently of them. The fact remains, however, that these manifestations accompanying the hot flushes have for some time been considered by many observers to be actual results of a deficiency of endocrine ovarian function. While Graves found that where, in the performance of hysterectomy, one or both ovaries were allowed to remain, no less than 81 per cent. of cases later developed hot flushes; he likewise found that in every instance subsequently reoperated the preserved ovaries were "densely adherent, degenerated, and cystic." This would suggest that the hot flushes are actually due to cessation of interstitial ovarian function. That this function persists even after the menopause—or cessation of the external secretory function of the ovary—is indicated by the clinical observation that hot flushes are frequently reported in patients whose ovaries are removed after the menopause has already been passed.

The symptoms belonging to the nervous and mental spheres, occurring after operative removal of the ovaries, are enumerated by Alfred Gordon[176] as: restlessness; difficulty in self-control; dissatisfaction with everything; difficulty in finding contentment in one's own efforts; want of interest in all absorbing subjects and objects; indifference, indolence, and pessimism; sometimes outbreaks of anger, with a tendency to attack.

Sleeplessness, functional digestive disturbances, headache, indefinite pains and paresthesias, and occasionally glycosuria and a tendency to obesity, may be accompanying symptoms. These conditions as a whole sometimes persist without change for a long period of time.

Menstrual disorders have been ascribed, in certain cases, to abnormalities of ovarian function. Here the difficulty is doubtless not with the interstitial tissue of the ovaries but with the corpus luteum. Novak[177] thinks that the amenorrhea of anemia, tuberculosis, and other debilitating conditions is possibly due to an inhibitory effect exerted upon the corpus luteum or, more probably, to failure of ovulation itself. He also looks upon hyperemia and hyperfunction of the ovaries, most often clinically manifest in excessive menstruation, as a factor contributing to the occurrence of fibrocystic disease of the ovaries. Hitschmann and Adler,[178] indeed, had already looked upon excessive menstruation as a result of inflammatory disease involving the ovaries.

Turenne[179] reports 4 cases of genital atrophy coupled with senile changes and appearance, following puerperal infection.

Diagnosis.—The presence of endocrine ovarian insufficiency is recognized through observation of the symptoms and signs previously mentioned. In the growing individual the chief evidences of the condition are poor development of the secondary sex characteristics, hypoplasia of the uterus and adnexa, and late menstruation. In middle adult life it is marked by menopause symptoms, especially hot flushes and nervous disturbances.

As Bandler has emphasized, the ovarian insufficiency may be either a primary disorder or the secondary result of an influence exerted upon the ovaries by the other endocrine organs, *viz.*, the thyroid, pituitary, adrenals, thymus, etc. In the later event stigmata of disordered function of these other glands may be apparent, and may facilitate and clarify the diagnosis. A persistent thymus may, according to Bandler, be indicated by the existence of hypoplastic ovaries.

Treatment.—As in the case of other ductless glands, administration of the dried substance of the insufficiently functionating ovary constitutes one of the most direct procedures at hand for relieving the symptoms produced. Although a complete agreement of opinion as to the efficacy of **ovarian opotherapy** has not as yet been secured, such medication is in general considered to be indicated for tardy and imperfect genital development in the female and for symptoms of the natural or of an artificial menopause later in life. Prolonged treatment is, as a rule, required. Bucura[180] gives ovarian extract intermittently, discontinuing it at first, for one week after from three to eight weeks' treatment, and later shortening the periods of medication until the drug is being taken for only one week in every month.

Numerous indications for ovarian treatment are recognized, *e.g.*, infantile and hypoplastic states of the generative organs, late menstruation, hot flushes or the psychoneurotic manifestations of the menopause, amenorrhea or oligomenorrhea (all cases of diminishing menstruation —Bandler), dysmenorrhea, sterility not due to pyogenic infection or to mechanical obstruction, insufficient compensatory activity of an ovary after its fellow has been removed, repeated abortions unassociated with disease or mechanical factors, hyperemesis during the early months of pregnancy, etc. Block and Llewellyn[181] call attention to the fact that hyposecretion of the ovary independently of the natural or surgical menopause may exist as a result of pelvic inflammatory disease, and report good results in the case of many patients of this group, as well as in frank menopause cases, following the administration of **corpus luteum extract** in doses of 2 grains (0.130 gram) or more, three times a day for from one to six months. Fishberg[182] notes that in some instances in which a relationship between asthmatic paroxysms and pregnancy or menstruation can be discerned, ovarian therapy favorably influences the asthma. In many cases of asthma occurring during the menopause, natural or artificial, ovarian substance of corpus luteum in moderate doses seems to act specifically, ameliorating the attacks as well as preventing their recurrence. This therapeutic indication appears to be all the more valuable in that most of these cases are peculiarly intolerant of opiates. So-called "essential hypogalactia" is actually, according to Coni Bazan,[183] a hypo-ovarian agalactia and is favorably influenced by corpus luteum or ovarian treatment, other coexisting symptoms of ovarian deficiency diminishing simultaneously.

That ovarian medication, to be fully effective, should comprise not merely the corpus luteum but also the interstitial cells, or at least their product, has been emphasized by Graves. Corpus luteum preparations are nevertheless still in widespread use. Morley[184] describes the employment of a water-soluble powder obtained from the corpus luteum which, he believes, yields therapeutic results more rapidly and permanently than the dried entire ovary. He reports good results from this product in the flushes of heat or cold, insomnia, and nervousness of the menopause, as well as in the amenorrhea or scanty menstruation. Iscovesco[185] employed with success in the same disturbances, and also in dysmenorrhea, chlorosis, and senile debility, a "lipoid" prepared by him from the ovary. A 2 per cent. oily solution of the product was given intramuscularly in doses of 1 mil daily; or from four to six pills, each containing 1/32 grain (0.02 gram) of the substance were administered by mouth.

Although, according to Graves, **transplantation** of sections of **healthy ovarian tissue** in the rectus muscle in cases subjected to oöphorectomy for pelvic disease had no marked effect upon the symptoms of the artificial menopause, other observers, especially Lydston,[186] have reported definite physiological effects from such a procedure, which, if successful, enable the patient to dispense with the constant ingestion of ovarian preparations. Lydston, in some of his cases, observed disappearance of such symptoms as hot flushes, sense of exhaustion, somnolence, stiffness of the knees, and sciatica, as well as improvement of the mental condition, following the transplantation. W. D. Phillips[187] has reported 12 cases of autogenous ovarian transplantation in which the grafts were embedded either in the abdominal adipose tissue over the rectus sheath, or beneath the rectus muscle, resting on the peritoneum. Of the 6 cases which were followed up, all were menstruating regularly, and in 3 cases the graft is stated to have been alive and functionating two years after operation. Apparently ovarian transplantation is a procedure deserving marked attention in the future, for both prophylactic and curative purposes.

Endocrinic Ovarian Overactivity

Instances of overproduction of the internal secretion of the ovaries probably occur both during the developmental and adult stages of life, but the resulting manifestations are less certainly known than are those of ovarian insufficiency.

Symptomatology.—It would appear that ovarian overactivity during the period of growth may be either primary, or secondary to hormonic influences exerted upon the ovaries by other endocrine glands, as in exophthalmic goiter, acromegaly, pineal disease, etc.

The most salient manifestation of this overactivity appears to be precocious menstruation, which may set in as early as the first year of life. Simultaneously there may also be an overdevelopment of the body as a whole, or premature secondary sex manifestations, *e. g.*, enlargement of the mammary glands, a female type of hirsuties, and unusual size of the external genitals, as well as, perhaps, premature change of the teeth and early closure of the epiphyses. In a case thus characterized, reported by Riedel, the underlying condition was found to be a sarcoma of the ovary; when this tumor was removed surgically, the precocious menstruation ceased.

In adults a form of menorrhagia with endometrial overgrowth has been ascribed to ovarian hyperactivity (Bandler). Frank[188] asserts that, aside from the time of puberty, ovarian overactivity occurs most often in the preclimacteric period. Hyperplasia of the uterine mucosa, thickening of the uterine muscle itself, and even fibroid uterine tumors have been ascribed to a functional hyperplasia of the ovaries. A form of metrorrhagia due to ovarian overactivity has also been described.

Treatment.—If excessive ovarian endocrine function is due, in a given case, to tumor of the ovary, **surgical removal** may be necessary, although in some instances **x-ray treatment** will be sufficient. The latter form of treatment might likewise prove adequate in overactivity unassociated with tumor, but the question whether the treatment might not exceed its object and cause a lasting ovarian inadequacy would have to be duly considered in its administration. To be sure, destruction of the function of the interstitial ovarian cells has seemed more difficult to obtain with the *x*-rays than arrest of ovulation—the external secretory function of the ovary. Where ovarian excess is secondary to secretory disturbance in other ductless glands, as already suggested, due endeavor should be made to remove the primary cause.

Pituitary substance, from ½ to 1 grain (0.0324 to 0.065 gram) three times a day, has been used by Block and Llewellyn[189] in profuse menorrhagia and metrorrhagia at puberty, on the ground that the pituitary secretion is antagonistic to that of the ovary in so far as its effect on the uterus is concerned. Prompt success attended the treatment, which also proved serviceable in a case of profuse menorrhagia in a young woman of twenty years. Some caution should be exercised in the use of large doses of pituitary (posterior lobe), as harmful results may follow a dosage in excess of the patient's needs. Bandler considers **thymus extract** useful in persistent menorrhagia or metrorrhagia following vaginal operation for prolapse of the uterus.

ENDOCRINIC DISORDERS OF THE TESTICLES

General Anatomy and Physiology.—Whereas the external secretion of the testicles, *viz.*, the spermatozoa, is conducted by definite lobules of glandular tissue known as the seminiferous organs, their internal secretion is considered to be produced in certain aggregations of polyhedral epithelial elements located in the loose connective tissue of the testicles and known as the interstitial cells of Leydig. These cells, yellowish in color, have been found experimentally to remain unaffected in spite of the induction of an artificial atrophy of the seminiferous tubules through ligation of the vasa deferentia, and to them the development and maintenance of the male secondary sexual characteristics are ascribed. That this view of an endocrine testicular function independent of spermatogenesis is valid has been proven by convincing experimental work, showing that atrophy of the seminiferous tubules fails to prevent development of male characteristics, provided the remaining tissues of the organs are allowed to remain or are implanted in the individual's tissues if wholly lacking.

Even through the administration of testicular extract it has proven possible to augment the male secondary sexual characteristics or to initiate their development where they have not previously existed, as in female animals. Apart from the influence of the testicular internal secretion on osseous metabolism, emphasized by Launois and Roy, a stimulating effect of testicular extracts on the neuromuscular apparatus has been shown to exist by means of ergographic experiments, in which injections of these extracts were found to reduce the fatigue of the nervous and muscular tissues which follows work, as well as to allay the subjective sensation of fatigue experienced by the subject under test.

The testicles contain a considerable amount of nucleoproteid material, as well as of lecithin, cholesterin, and inorganic salts. Spermin, an organic base which is also present, was held by Poehl to be the main endocrine product of the organ, and to have the power to accelerate oxidation in the living tissues or to act as a carrier of oxygen. Pantchenko has credited spermin with a catalytic, oxidative property. The product has been shown, however, to exist in localities other than the testicles, *viz.*, in the nervous tissues and, indeed, according to Dixon in all body tissues. According to C. E. deM. Sajous, spermin is not a specific testicular product, but is in many respects analogous to the adrenal principle, to which he ascribes an important rôle in the carrying of oxygen to the body tissues.

ENDOCRINIC TESTICULAR INSUFFICIENCY

Deficient functioning of the interstitial tissue of the testicles constitutes a definite, separate, disorder which requires entirely different clinical consideration from arrest of spermatogenesis, due to disease of the seminiferous tubules. Such insufficiency may vary markedly in degree, ranging from a slight deficit which, in all ordinary aspects, fails to differentiate the subject definitely from the usual type of male human being, to a complete lack of interstitial secretion, as a result of which all normal characteristics of the male are in abeyance. The extent to which the disturbance may become established depends markedly upon the age of the subject at the time of failure of the endocrine testicular function, many characteristics acquired during the period of normal development persisting in spite of testicular insufficiency where the latter supervenes at an advanced age.

Etiology.—Diminution or cessation of the interstitial function may result from trauma of the testicles at any period of life. Diseased conditions of these organs, due, for instance, to syphilitic, gonococcal, or tuberculous infection, or the atrophy following orchitis in epidemic parotitis, may also be responsible. As in the case of the ovaries, moreover, diminished testicular function may occur as a secondary accompaniment of primary disease of some other ductless gland, *e.g.*, of the pituitary body in dystrophia and adiposogenitalis.

Symptomatology.—Where a male child suffers injury or disease of the testicles constituting essentially a castration, failure of development of the sexual organs and of the male secondary sex characteristics results from that time on. Impotence and loss of sexual desire are caused by castration at any period before sexual development has been completed. Where the endocrine function is destroyed before puberty the voice remains high-pitched throughout life, the beard fails to grow, the skin remains soft and white, and in many instances there is a tendency to general fat deposition, the adipose tissue being, moreover, so distributed as to establish the rounded curves of the female outline. The subject's stature is often above normal, the long bones of the limbs growing to greater length than the normal, while the muscles fail to enlarge to the extent customary in male individuals. A reversion toward the female type is seen in the relatively large size of the breasts. The mental condition is characterized by lack of initiative, submissiveness or cowardice, an even, somewhat indifferent disposition, pessimism, and, sometimes, a relatively low grade of intelligence or dullness.

Where sex development has been completed before the cessation of endocrine function, or where the loss of this function has been only partial, a eunuchoid state results, in which many of the sex features associated with castration are present in a mitigated and less manifest form. Sexual desire and potency may be only slightly affected for a time, dwindling only gradually, in the course of a number of years. Partial atrophy of the penis and other sexual organs may likewise eventually occur. Certain of the secondary sex characteristics are more or less plainly involved, mammary overdevelopment occurring, the skin remaining smooth, the beard scanty, and a tendency to fat deposition being apparent. The stature, however, may not be unusual, ossification of the epiphyses of the long bones having already taken place before the endocrine failure, and the voice being of low pitch, having "changed" at puberty.

Treatment.—Endocrinic testicular insufficiency may be counteracted, at least partly, by the administration of **testicular extract** or by **transplantation of testicular tissue.**

It has been claimed that **spermin** improves general tissue oxidation in these cases and exerts a tonic action on the circulation. In general, however, the use of an extract of the whole testicle has seemed more effective. Where the impairment of the interstitial testicular function has occurred only after puberty, distinct results are obtainable from this measure in overcoming the lack of mental alertness, sluggishness of the circulation, and impairment of certain reflex functions, commonly met with in these subjects. Improvement of metabolic activity very definitely results from the administration of testicular extract, although, in cases of castration occurring before puberty, development of the lacking male secondary sex characteristics is hardly to be expected. The effects of testicular organotherapy are not as positive and all-sufficient as are those of thyroid medication in hypothyroidia. Lespinasse specifies that in the administration of desiccated animal testes, large amounts are required.

Moderate doses of **thyroid substance** seem advantageous in combination with the testicular extract, in these cases, as they assist in overcoming the sluggish metabolism and tendency to excessive fat deposition. According to Stelwagon,[190] extracts of the anterior lobe of the **pituitary body** exert a favorable effect upon the male reproductive organs, and such extracts might be combined with the testicular treatment. **Extract of the adrenal cortex** might also prove serviceable.

The benefits to be derived from testicular transplantation in cases of interstitial inadequacy—benefits manifestly far superior to those conferred by the ingestion of testicular preparations—have been well shown by clinical experience in this and other countries. In this field Lydston,[191] in particular, has accomplished important work, although in 1913 Lespinasse had already reported a case of impotence promptly relieved by implantations in the scrotum and rectus muscle of slices of testicular tissue from a living subject.

That implanted human sexual glands may survive and acquire a new circulation, and that glands from dead bodies may be successfully used for this purpose has been shown by Lydston's clinical studies. Glandular tissue from a living subject being rarely obtainable, it is important to know that refrigeration for from twenty-four to forty-eight hours before implantation does not lessen the viability of tissue from dead bodies. Lydston found it possible to implant an entire human testis with some measure of success, and believes that in addition to its use in cases of impotence, implantation, with or without anastomosis of the seminal ducts with the vas deferens, may have a certain range of usefulness in sterility. In at least one of his cases testicular implantation showed a favorable influence in leading to the establishment of male secondary sex characteristics, in spite of the complete destruction of the testicles before puberty. This is a searching test of the efficacy of the procedure, as such an effect has been found to require a much larger dosage of the testicular endocrine product than the preservation of virility after the latter has once been established. Lydston makes special reference to the general physiologic efficiency, and hence individual and social efficiency, resulting from testicular implantation. He believes that the procedure will probably prove useful in sexual inversions or perversions and in cases of cryptorchidism and imperfect testicular development or atrophy from disease.

A case of implantation for bilateral testicular atrophy following orchitis in mumps has been reported by Robert T. Morris.[192] The organs had been lost at the age of 13, and the implantations, into the rectus muscle as well as into the scrotum, were made at the age of 27. Wedge-shaped pieces of testicle 3 millimeters thick were implanted. Among other results, the vestige of atrophied testicle remaining showed considerable enlargement, as did likewise the epididymis and spermatic cord. Sexual function was stimulated, but no change took place in the patient's youthful voice; in this case, however, the graft had been taken from a patient 54 years old. Full and frequent morning erections appeared, and the previously small penis increased in size.

Congenital and acquired hypoplasia of the testicle are, according to Lespinasse,[193] the only types of impotence which should be treated by testicular transplantation. Two technics of transplantation are available—*en masse* and by morcellation. The latter is used exclusively by Lespinasse. Transplantation with blood-vessel anastomosis has not proven clinically practicable. Nevertheless, the results of transplantation are remarkable in some cases.

ENDOCRINIC TESTICULAR OVERACTIVITY

Judging from the clinical evidences of the opposite state—endocrinic testicular insufficiency—the manifestations of this condition should be abundant facial hirsuties, absence of fat deposition about bony eminences, a rough skin, marked lack of mammary development, heavy musculature and great strength, combativeness, and sexual proclivities above the average. Beyond such a mere statement of apparently reasonable possibilities, however, nothing can as yet be said concerning the condition. Satyriasis seems in most instances, if not always, to be due to causes other than interstitial overactivity. The sexual precocity at times observed in cases of hypernephroma or pineal tumors is doubtless associated with an excessive activity of the testicular interstitial tissue.

Treatment.—In general, the treatment of this condition would be merely palliative, although in some instances more radical measures might seem advisable. The **bromids** would probably be helpful, as might also a pronounced **reduction in the amount of meat in the diet.** Where such palliative measures prove insufficient, **x-ray treatment** might be of service in attenuating the interstitial function. **Surgical measures** would often be indicated in the presence of some tumor situated elsewhere, and apparently primary to the endocrine testicular disturbance.

REFERENCES

1. Vincent, S. Recent views as to the function of the adrenal bodies. Endocrinology, Glendale, Cal., 1917, i, 140-152.
2. Marie, A. Activation de la toxine tétanique. Ann. de l'Inst. Pasteur, 1914, xxviii, No. 1, pp. 1-5.
3. Gruber, C. M. Further studies on the effect of adrenalin upon blood flow in muscles. Amer. Jour. Physiol., 1918, xlv, 302-313.
4. Gunning, R. E. L. Effects of adrenin on the urine flow of anesthetized and unanesthetized dogs. Amer. Jour. Physiol., 1918, xlv, 528-534.
5. Addis, Barnett and Shevky. The regulation of renal activity. Amer. Jour. Physiol., 1918, xlvi, 39-62.
6. Loeper and Verpy. L'action de l'adrénaline sur le tractus digestif. Compt. rend. de la Soc. de biol., 1917, lxxx, 703-705.
7. Gruber and Kretschmer. Effect of adrenalin upon the fatigue produced by the injection of fatigue products, lactic acid, and acid potassium phosphate. Amer. Jour. Physiol., 1918, xlvii, 178-184.
8. Hartman, Kilborn and Fraser. Adrenalin vasodilator mechanisms. Amer. Jour. Physiol., 1918, xlvi, 502-525.
9. Kramer, D. Das Verhalten des sympathischen Nervensystems bei den Erkrankungen im Säuglingsalter. Der Adrenalingehalt der Säuglingsnebenniere. Monatschr. f. Kinderheilk., 1917-18, xiv, 531-546.
10. Harris, D. T. Some observations on the recent influenza epidemic. Lancet, 1918, ii, 877.
11. Richards, O. Growths of the kidney and adrenals. Guy's Hosp. Reports, 1905, lix, 217-332.
12. Bra. Cited by Adams, E. W. The results of organotherapy in Addison's disease. Practitioner, 1903, lxxi, 472-502.
13. Jaboulay. La greffe de corps thyroide et de capsules surrénales dans les maladies de ces glandes. Lyon méd., 1897, lxxxiv, 399-400.
14. Courmont. Congr. de méd. int., Montpellier, 1898.
15. Bohr and Henriques. Recherches sur le lieu de la consommation de l'oxygène et de la formation de l'acide carbonique dans l'organisme. Arch. de physiol., 1897, ix, 459-474.
    Comparaison des quotients respiratoires déterminés simultanément dans le sang et dans l'air expiré. *Ibid.,* 1897, ix, 819-831.
16. Pembrey. Recent advances in physiology and biochemistry. 1906, p. 549.
17. Bohr, C. Ueber die Lungenathmung. Skand. Arch. f. Physiol., 1891, ii, 236-268.
18. Haldane and Smith. The absorption of oxygen by the lungs. Jour. Physiol., 1897, xxii, 231-258.
19. Harley, V. The effect of compression on one lung on respiratory gas exchange. Jour. Physiol., 1899-1900, xxv, 33-48.

20. Gottschau, M. Struktur und embryonale Entwickelung der Nebennieren bei Säugethieren. Arch. f. Anat. u. Physiol., Anat. Abt., 1883, 412-458.
21. Manasse, P. Ueber die Beziehungen der Nebennieren zu den Venen und dem venösen Kreislauf. Arch. f. Path. u. Physiol., 1894, cxxxv, 263-276.
22. Aulde, A. G. Preliminary report on the suprarenal gland, and the causation of Addison's disease. Brit. Med. Jour., 1894, i, 1017-1018.
23. Stilling, H. Zur Anatomie der Nebennieren. Arch. f. path. Anat., 1887, cix, 324-346.
24. Stoerk and Von Haberer. Beitrag zur Morphologie des Nebennierenmarkes. Arch. f. mikrosk. Anat., 1908, lxxii, 481-496.
25. Pfaundler, M. Zur Anatomie der Nebenniere. Sitzungsber, d. k. Akad. d. Wissensch. Math.-natura clin., 1892, cl, 515-553.
26. Cybulski and Szymonowicz. On the functions of suprarenal bodies. Gaz. Lekarska, 2nd Ser., 1895, xv, 299-308; Archiv f. d. gesammte Physiol., 1896, lxiv, 97-164.
27. Bert, P. Sur l'état dans lequel se trouve l'acide carbonique du sang et des tissus. Compt. rend. de l'Acad. des Sc., 1878, lxxxvii, 628-630.
28. Vulpian. Note sur quelques reactions propres à la substance des capsules surrénales. Compt. rend. de l'Acad. des Sc., 1856, xliii, 663-665.
29. Cybulski, N. On the functions of suprarenal bodies. Gaz. Lekarska, 2nd Ser., 1895, xv, 299-308.
30. Battelli, M. F. Transformation de l'adrénaline "in vitro." Compt. rend. Soc. de biol., 1902, liv, 1435-1436.
31. Menten, M. L. Action of adrenalin on the blood. Amer. Jour. Physiol., 1917, xliv, 176-195.
32. Byelaventz, P. P. Action of adrenalin on living organism. Russk. Vrach, 1903, ii, 247.
33. Bernstein and Falta. Über die Einwirkung von Adrenalin, Pituitrinum infundibulare und Pituitrinum glandulare, auf den respiratorischen Stoffwechsel. Verhandl. d. deut. Kongr. f. inn. Med., 1912, xxix, 536-540.
34. Nice, Rock and Courtright. The influence of adrenalin on respiration. Amer. Jour. Physiol., 1914, xxxiv, 326-331.
35. Oliver and Schäfer. The physiological effects of extracts of the suprarenal capsules. Jour. Physiol., 1895, xviii, 230-276.
36. Reichert, E. T. Adrenalin, the active principle of adrenal extract, a proposed agent in morphin- and opium-poisoning, in circulatory failure, in the prevention of collapse in anesthesia, and in allied conditions. Univ. Penn. Med. Bull., 1901-1902, 51-54.
37. Lépine, R. Sur l'action de l'extrait de capsules surrénales. Semaine méd., 1903, xxiii, 53-56.
38. Menten and Crile. Studies on the hydrogen-ion concentration in blood under various abnormal conditions. Amer. Jour. Physiol., 1915, xxxviii, 225-232.
39. Menten. *Loc. cit.* (*see* ref. No. 31).
40. Stewart and Rogoff. The spontaneous liberation of epinephrin from the adrenals. Jour. Pharm. and Exper. Therap., 1916, viii, 479-524.
41. Bunge and Schmiedeberg. Ueber die Bildung der Hippursäure. Arch. f. exper. Path. u. Pharm., 1876, vi, 233-255.
42. Jaquet, A. Ueber die Bedingungen der Oxydationsvorgänge in den Geweben. Arch. f. exper. Path. u. Pharm., 1892, xxix, 386-396.
43. Abelous and Biarnès. Sur le pouvoir oxydant du sang et des organes. Arch. de physiol. norm. et path., 1895, 5ième Sér., vii, 195-199.
    Recherches sur le mécanisme des oxydations organiques. *Ibid.*, 1895, 5ième Sér., vii, 239-244.
44. Jolles, A. Beiträge zur Kenntniss der Blutfermente. Münch. med. Wchnschr., 1904, li, No. 2, 2083-2085.

45. Poehl, A. V. New data on the chemical processes of life in connection with the question of the value of adrenalin. Jour. Med. Khim. i Organoterap., St. Petersburg, 1903, ix, 19-30.

46. Mackenzie, G. M. The suprarenal system and carbohydrate metabolism. Arch. Int. Med., 1917, xix, 593-610.

47. Sajous, C. E. de M. Internal secretions and the principles of medicine, Philadelphia, 1916, i, 70.

48. Gaskell, G. F. The chromaffine system of annelids and the relations of this system to the contractile vascular system in the leech, Hirudo medicinalis. Phil. Trans. Royal Soc., London, 1914, ccv, 153-211.

49. Sajous, C. E. de M. *Loc. cit.* (*See* ref. No. 47), 1903, ii, 1215.

50. Gley, E. Du rôle des glandes surrénales dans l'action des substances vaso-constrictives. Les substances vaso-constrictives indirectes. Compt. rend. de l'Acad. des Sc., 1914, clviii, 2008-2011.

51. Cannon and Cattell. Studies on the conditions of activity in endocrine glands. Amer. Jour. Physiol., 1916, xli, 74-78.

52. Wheeler and Vincent. Trans. Royal Soc., Canada, 1917, ii, 125.

53. Voegtlin and Macht. Isolation of a new vasoconstrictor substance from the blood and the adrenal cortex. Jour. Amer. Med. Assn., 1913, lxi, 2136-2138.

54. Iscovesco. Nouvelles recherches sur les propriétés homo- et hétéro-stimulantes de certains lipoides (testicule, thyroide, hypophyse, sang, surrénales). Bull. et mém. de la Soc. méd. des hôp. de Paris, 1912, xxxiv, 758-768.

55. Vincent, S. The experimental and clinical evidence as to the influence exerted by the adrenal bodies upon the genital system. Surg., Gynec. and Obstet., 1917, xxv, 294.

56. Lorand, A. Old age deferred. Amer. Ed., Philadelphia, 1910, 111.

57. Carl, W. Das chromaffine System and seine Erschöpfung durch Muskelarbeit. Deut. med. Wchnschr., 1911, xxxvii, 1827-1829.

58. Sampaio, O. Contribuiçae paro o estudo do valor da docimasia pararenal na diagnose da morte subito. Brazil méd., 1918, xxxii, 91, 90.
   Parecer medico-legal sobre um ferrimento por faca no thorax. *Ibid.*, 173.

59. Lucksch. Adrenalin content of the adrenals in various fatal diseases. Corresp.-Bl. f. schweiz. Aerzte; quoted in Med. Rec., 1917, xcii, 791.

60. Carles, J. L'insuffisance surrénale chez le combattant. Jour. de méd. de Bordeaux, 1918, lxxxix, 185-188.

61. Merklen and Malloizel. Suprarenalitis. Paris méd., 1918, viii, 233.

62. Loeper. Études sur la pathologie du soldat. Jouve, Paris, 1917.

63. Lautier and Grégoire. La ligne blanche dite surrénale; recherches cliniques. Compt. rend. de la Soc. de biol., 1910, lxviii, 690.

64. Baudron. La ligne blanche surrénale dans l'armée. Caducée, 1918, xviii, 93.

65. Ravaut and Krolunitsky. Oreillons et méningite cérébro-spinale a paraméningocoques. Guérison par injections intrarachidiennes lombaires et cervicales de sérum antiparaméningococoquique de Dopter. Apparition transitoire du syndrome Froin. Soc. méd. des hôp. de Paris, 1915, 3ième Série, xxxix, 618-624.
   Insuffisance surrénale aigue guérie par l'adrénaline. Raie blanche surrénale. Recherches sur sa valeur clinique. *Ibid.*, 624-629.

66. Carles. *Loc. cit.* (*See* ref. No. 60).

67. Josué, O. Traitement de l'insuffisance surrénale. Paris méd., 1917, vii, 13-18.

68. Satre, A. L'insuffisance surrénale des soldats en campagne. Jour. de méd. de Paris, 1918, xxxvii, 67-73; 87-93.

69. Landau, E. Altersveränderungen des Venensystems der Nebennieren. St. Petersb. med. Wchnschr., 1908, xxxiii, 249-250.

70. Minervini, R. Des capsules surrénales. Développement—structure—fonctions. Jour. d'anat. et de physiol., 1904, 449-492; 634-667.

71. Rashbrook and Carter. A case of hypoadrenia simulating intestinal obstruction. Lancet, 1918, ii, 240.
72. Comessatti. Adrenalina surrenale (Dosamente sistematici dell') nella patologia dell'nomo. Riv. crit. di clin. med., 1910, xi, 49.
73. Goldzieher, M. Beiträge zur Pathologie der Nebennieren. Wien. klin. Wchnschr., 1910, xxiii, 809-812.
74. Nuñez. Anales de la Fac. de Med. de Montevideo, Sept.-Oct., 1918.
75. Dumas and Hervier. Du rôle des dégénérescences des capsules surrénales et des parenchymes glandulaires dans certain syndromes terminaux des infections graves. Bull. et mém. de la Soc. méd. des hôp. de Paris, 1912, xxviii, 28-46.
76. Dujarric de la Rivière et Villerval. Dysentérie amibienne autochtone à forme surrénale. Paris méd., 1917, vii, 310-312.
77. Naamé. Insuffisance surrénale et adrénaline; choléra et mal de mer. Paris méd., 1917, vii, 415-416.
78. Paisseau and Lemaire. De l'insuffisance surrénale dans le paludisme. Presse méd., 1916, xxiv, 545-547.
79. Portocalis, A. Acute suprarenal insufficiency in infectious diseases. Medico-Surg. Soc. of Greece; Jour. Amer. Med. Assn., 1918, lxxi, 767.
80. Sergent, E. Importance de la notion d'insuffisance surrénale et du rôle de l'opothérapie surrénale en médecine et en chirurgie d'armée. Bull. de l'Acad. de méd., 1915, lxxiv, 268-271.
81. Sanchez Moreno, A. Sobre un caso de insufficiencia suprarénal de forma pseudo-meningea. Cronica méd., Lima, 1918, xxxv, 17-19.
82. Sergent. *Loc. cit.* (*See* ref. No. 80).
83. Brindeau, A. Mort subite post-opératoire et tuberculose des surrénales. Arch. mens. d'obstét. et de gynéc., 1917, ix, 159-168.
84. Sydenstricker, Delatour and Whipple. The adrenalin index of the suprarenal glands in health and disease. Jour. Exper. Med., 1914, xix, 536-551.
85. Cooke, J. V. Some observations on the blood-pressure-raising substance of the adrenals in acute adrenal insufficiency. Arch. Int. Med., 1912, ix, 108-113.
86. Mansvetova, S. M. Influence of subcutaneous injections of adrenalin upon blood-pressure in typhoid fever and pneumonia. Russk. Vrach, 1914, xiii, 874-877.
87. Sergent. *Loc. cit.* (*See* ref. No. 80).
88. Moltschanoff, W. Zur Frage über die Rolle der Nebennieren in der Pathologie und Therapie der Diptherie und anderen Infektionskrankheiten. Jahrb. f. Kinderheilk., 1912, lxxvi, 200-222.
89. Goormaghtigh, N. Contribution à l'étude du fonctionnement de la capsule surrénale humaine dans les états infectieux. Arch. méd. belges, 1917, lxx, 697.
90. Josué. *Loc. cit.* (*See* ref. No. 67).
91. Brindeau. *Loc. cit.* (*See* ref. No. 83).
92. Hutinel, V. Scarlatine maligne et syndrome malin dans les maladies infectieuses. Arch. de méd. des enf., 1915, xviii, 125-153.
93. Rohmer, P. Ueber Adrenalin-Pituitrinbehandlung. Münch. med. Wchnschr., 1914, lxi, 1336-1337.
94. Moschcowitz, E. Focal necrosis of the adrenal gland; with remarks upon acute adrenal insufficiency. Amer. Jour. Med. Sci., 1918, clvi, 313-329.
95. Reich and Beresnegowski. Untersuchungen über den Adrenalingehalt der Nebennieren bei akuten Infektionen, besonders Peritonitis. Beitr. z. klin. Chir., 1914, xci, 403-434.
96. Remlinger and Dumas. Syndrome capsulaire aigu au cours de la dysentérie bacillaire. Ann. de méd., 1915, ii, 605-626.
97. Kindley, G. C. The adrenals in acute infections. Texas State Jour. Med., 1914-1915, x, 195-198.

98. Bittorf. Die Pathologie der Nebennieren und der Morbus Addisonii. Jena, 1908.
99. Mackenzie, G. M. The suprarenal system and carbohydrate metabolism. Arch. Int. Med., 1917, xix, 593-610.
100. Porges, O. Zur Pathologie des Morbus Addisonii. Zeitsch. f. klin. Med., 1910, lxx, 243-250.
101. Von Neusser and Wiesel. Die Erkrankungen der Nebennieren. Vienna, 1910.
102. Leonardi, E. Il morbo di Addison e le secrezioni interne. Policlinico, 1909, 354-364.
103. Lippmann, A. Ein Beitrag zum "akuten" Morbus Addisonii. Med. Klin., 1913, ix, 535-537.
104. Kaplan and Greeff. Adrenopathic hyperchlorhydrias. New York Med. Jour., 1918, cviii, 61-64.
105. Morton, D. M. Addison's disease: Treatment by transplantation of suprarenal glands. Austral. Med. Jour., 1912, ii, n.s., 573-574.
106. Bate, R. A. Suprarenal extract in the treatment of Addison's disease. Amer. Pract. and News, 1899, xxviii, 90-91.
107. Suckling, C. W. The treatment of Addison's disease with suprarenal gland substance. Brit. Med. Jour., 1898, i, 1388.
108. Osborne, O. T. Two cases of suprarenal disease. Amer. Jour. Med. Sci., 1918, clvi, 202-205.
109. Satterthwaite, T. E. Some internal secretions and the heart. Med. Times, 1917, xlv, 128-130.
110. Josué. *Loc. cit.* (*See* ref. No. 67).
111. Ramond and François. L'Addisonisme de guerre. Bull. et mém. de la Soc. méd. des hôp. de Paris, 1917, xli, 3 sér., 1001-1003.
112. Goormaghtigh. *Loc. cit.* (*See* ref. No. 89).
113. Lesné and François. Insuffisance surrénale au cours de l'érysipèle du nouveau-né. Paris méd., 1912, vii, 119.
114. Arnaud, F. Les hémorrhagies des capsules surrénales. Arch. gén. de méd., 1900, clxxxvi, 5-65.
115. Lavenson. Acute insufficiency of the suprarenals. Arch. Int. Med., 1908, ii, 62-73.
116. Kuttner. Erfolgreiche Exstirpation einer grossen Struma suprarenalis cystica haemorrhagica mitsamt der Nebenniere. Versamml. deut. Natur. u. Aerzte; Münch. med. Wchnschr., 1912, lix, 2422.
117. Trotter, W. Clinical lecture on hypernephroma. Lancet, i, 1581-1586.
118. Scudder, C. L. Bone metastases of hypernephroma. Annals of Surg., 1906, xliv, 851-865.
119. Gelle, E. Quatre cas de tumeur rénale d'origine surrénalienne. Echo méd. du nord., 1908, xii, 369-378.
120. Israel, J. Zur Diagnose der Nebennierengeschwülste. Deut. med. Wchnschr., 1905, xxxi, 1745-1749.
121. Tuffier. Le virilisme surrénal. Bull. de l'Acad. de méd., 1914, lxxi, 726-731.
122. Michon, M. E. Tumeur de la glande surrénale à évolution maligne. Extirpation. Guérison opératoire par M. Veinin. Bull. et mém. de la Soc. de chir. de Paris, 1913, xxxix, 1764-1769.
123. Hammar, J. A. Zur Histogenese und Involution der Thymusdrüse. Anat. Anzeig., 1905, xxvii, 23-30; 41-89.
124. Dustin, A. P. Quelques mots à propos du thymus humain. Ann. et Bull. de la Soc. Roy. des Sci. méd. et nat. de Bruxelles, 1919, No. 2, 30-31.
125. Biedl. Internal secretory organs. New York, 1913, 112.
126. Huiskamp, W. Ueber die Eiweisskörper der Thymusdrüse. Zeit. f. physiol. Chemie, 1901, xxxii, 145-196.
127. Sajous. *Op. cit.* (*See* ref. No. 47), 1903, i, 182.

128. Pappenheimer, A. M. The thymus gland and its possible relation to the female genital tract. Surg., Gynec. and Obstet., 1917, xxv, 276-283.
129. Dustin. *Loc. cit.* (*See* ref. No. 124).
130. Paton and Goodall. Contribution to the physiology of the thymus. Jour. Physiol., 1904, xxxi, 49-64.
131. Hoskins, E. R. Is there a thymic hormone? Endocrinology, 1918, ii, 241-257.
132. Ver Eecke, A. Structure et modifications fonctionnelles du thymus de la grenouille. Bull. de l'Acad. Roy. de méd. de Belgique, 1899, xiii, 67-86.
133. Hart and Nordmann. Experimentelle Studien über die Bedeutung der Thymus für den tierischen Organismus. Berl. klin. Wchnschr., 1910, xlvii, 814-817.
134. Lanzarini, F. Grave osteoporosi infantile associata a sclerosi del timo. Riv. di clin. pediat., 1916, xiv, 393-418.
135. Ogata, M. Beiträge zur Kenntniss des thymotoxischen Serums. Acta. Scholae. med. univ. imp. Kioto, 1917, i, 449-472.
136. Morel, L. Syndromes thymiques. Paris méd., 1914, xiii, 161-165.
137. Müller. Zeitsch. f. Biol., 1917, lxvii, 489.
138. Del Campo, E. Fortgesetzte Untersuchungen über die neue Funktion des inneren Sekretes der Thymusdrüse. Zeitsch. f. Biol., 1917-18, lxviii, 285-300.
139. Bell, E. T. Tumors of the thymus in myasthenia gravis. Jour. Nerv. and Mental Dis., 1917, xlv, 130-143.
140. Haneborg, A. O. Chorea. Norsk Mag. f. Laegevidensk., 1916, lxxvii, 1040.
141. Ludlum and Corson-White. The thymus and pituitary in dementia precox. Physiological characteristics in insanity. Amer. Jour. Insanity, 1915, lxxi, 733-745.
142. Sajous. *Op. cit.* (*See* ref. No. 47), 1916, i, 289.
143. Leeper, B. C. A. Mongols. Rev. Neurol. and Psychiat., 1912, x, 11-20.
144. Taguchi. Kyoto Igak Kwai Zashi, 1917, xiv, 1.
145. Gismondi, A. Contributo allo studio e alla terapia dell'ipertrofia timica. Gazz. d. osp. e d. clin., 1916, xxxvii, 1634-1637.
146. Hammar. Svenska Lak. Handling, Sept., 1916.
147. Symmers, D. Status lymphaticus. Amer. Jour. Med. Sci., 1918, clvi, 40-59.
148. Benjamin and Lange. Report of 19 cases of hyperplasia of the thymus gland, treated by the *x*-rays. Arch. of Pediat., 1918, xxxv, 70.
149. Gismondi. *Loc. cit.* (*See* ref. No. 145.)
150. Friedlander, A. Enlargement of the thymus treated by the Roentgen rays. Amer. Jour. Dis. of Child., 1917, xiv, 40-46.
151. Benjamin and Lange. *Loc. cit.* (*See* ref. No. 148).
152. Cook, P. H. Roentgenotherapy in hypertrophy of the thymus gland. Boston Med. and Surg. Jour., 1916, clxxv, 483-489.
153. Crotti, A. Thyroid and thymus, 1918, i, 556.
154. Parker, C. A. Surgery of the thymus gland. Thymectomy. Report of 50 operated cases. Amer. Jour. Dis. of Child., 1913, v, 89-121.
155. Dock, G. The thymus gland. Ohio State Med. Jour., 1915, xi, 555-562.
156. Jordan, H. E. The histogenesis of the pineal body of the sheep. Amer. Jour. Anat., 1911, xii, 249.
157. Ramon y Cajal. Apuntes para el studio del bulbo requideo cerebelo y origen de los nervios encefalicos. Soc. Españ. Hist. Nat., Madrid, 1895.
158. Horrax, G. Studies on the pineal gland. Arch. Int. Med., 1916, xvii, 607-645.
159. Pellizzi, G. B. La sindrome epifisaria "macrogenitosomia precose." Riv. ital. d. neuropatol., 1910, iii, 193-207; 250-272.

160. DANDY, W. E. Extirpation of the pineal body. Jour. Exper. Med., 1915, xxii, 237-247.
161. MCCORD, C. P. The influence of the pineal gland upon growth and differentiation with particular reference to its influence upon prenatal development. Surg., Gynec. and Obstet., 1917, xxv, 250-260.
162. HOSKINS, E. R. The growth of the body and organs of the albino rat as affected by feeding various ductless glands (thyroid, thymus, hypophysis, and pineal). Jour. Exper. Zoöl., 1916, xxi, 295-346.
163. MCCORD and ALLEN. Evidences associating pineal gland function with alterations in pigmentation. Jour. Exper. Zoöl., 1917, xxiii, 207-224.
164. MARBURG, OTTO. Zur Frage der Adipositas universalis bei Hirntumoren Wien. med. Wchnschr., 1907, lvii, 2511-2515.
165. BAILEY and JELLIFFE. Tumors of the pineal body. Arch. Int. Med., 1911, viii, 851-880.
166. TIMME. Progressive muscular dystrophy as an endocrine disease. Arch. Int. Med., 1917, xix, No. 1, 79-104.
167. UREMURA. Zeitsch. f. Pathol., 1917, xx, No. 3.
168. DANA, BERKELEY, GODDARD and CORNELL. The functions of the pineal gland, with reports of feeding experiments. Med. Rec., 1913, lxxxiii, 835-847.
169. LOEB, L. The relation of the ovary to the uterus and mammary gland from the experimental aspect. Surg., Gynec. and Obstet., 1917, xxv, 300-315.
170. LOEWY and RICHTER. Zur wissenschaftlichen Begründung der Organotherapie. Berl. klin. Wchnschr., 1899, xxxvi, 1095-1100.
171. MURLIN and BAILEY. Relation of the sex glands to metabolism. Surg., Gynec. and Obstet., 1917, xxv, 332-336.
172. GRAVES, W. P. Ovarian organotherapy. Trans. Amer. Med. Assn.; New York Med. Jour., 1917, cv, 1262.
173. BANDLER, S. W. The ductless glands in gynecology. Amer. Jour. Obstet., 1917, lxxvi, 644.
174. BANDLER. *Loc. cit.*
175. GRAVES, W. P. Transplantation and retention of ovarian tissue after hysterectomy. Surg., Gynec. and Obstet., 1917, xxv, 315-323.
176. GORDON, A. Nervous and mental disturbances following castration in women. Jour. Amer. Med. Assn., 1914, lxiii, 1345-1348.
177. NOVAK, E. The corpus luteum, its life cycle and its rôle in menstrual disorders. Jour. Amer. Med. Assn., 1916, lxvii, 1285-1291.
178. HITSCHMANN and ADLER. Ein weiterer Beitrag zur Kenntnis der normalen und entzündeten Uterusmucosa. Die Klinik der Endometritis mit besonderer Berücksichtigung der Endometritis mit besonderer unregelmässigen Gebärmutterblutungen. Arch. f. Gynäk., 1913, c, 233-304.
179. TURENNE, G. Senilidad prematura y atrofia genital. Rev. méd. del Uruguay, 1917, xx, 742-751.
180. BUCURA, C. B. Praktische Ergebnisse aus unseren heutigen Anschauungen über die endokrine Tätigkeit des Eierstockes. Zentralbl. f. Gynäk., 1916, xl, 816-819.
181. BLOCK and LLEWELLYN. Organotherapy in gynecology. Amer. Jour. Obstet., 1917, lxxv, 357.
182. FISHBERG, M. Treatment of certain forms of asthma with ovarian substance and corpus luteum. Med. and Surg., 1918, ii, 26-34.
183. BAZAN, F. A. CONI. La función endocrina del ovario y la secreción mammaria. Sem. méd., Buenos Aires, 1918, xxv, 570.
184. MORLEY, W. H. The therapeutic application of ovarian extract. Jour. Mich. State Med. Soc., 1916, xv, 372-377.
185. ISCOVESCO, H. Les lipoides de l'ovaire du corps jaune et du testicule. Presse méd., 1912, xx, 845-847.

186. Lydston, F. Impotence and sterility, with aberrations of the sexual function and sex-gland implantation. Chicago, 1917.
187. Phillips, W. D. Ovarian transplantation. Report of cases. Texas State Jour. Med., 1916-1917, xii, 213-217.
188. Frank, R. T. Symposium on the relation of the glands of internal secretion to gynecology and obstetrics. Surg., Gynec. and Obstet., xxv, 225-229.
189. Block and Llewellyn. *Loc. cit.* (*See* ref. No. 181).
190. Stelwagon, T. C., Jr. Impotence in the male. New York Med. Jour., 1916, civ, 879.
191. Lydston. *Loc. cit.* (*See* ref. No. 186).
192. Morris, R. T. A case of testicle grafting with unexpected results. Jour. Amer. Med. Assn., 1916, lxvii, 741-742.
193. Lespinasse, V. D. Impotency: Its treatment by transplantation of testicle. Surg. Clinics, Chicago, 1918, ii, 281-288.

CHAPTER II

DISEASES OF THE THYROID AND PARATHYROID GLANDS

By Charles E. De M. Sajous, M.D., LL.D., Sc.D.,F.A.C.P.

Functions of the thyroid gland and parathyroid glandules, p. 197—Functions of the parathyroids, p. 201.
Goiter (Struma, bronchocele), p. 204:—Etiology and pathogenesis, p. 204; Symptomatology, p. 208—Non-toxic goiter, p. 210:—Types and prognosis, p. 210:—Non-toxic parenchymatous goiter, p. 210; Non-toxic nodular goiter, p. 211—Pressure symptoms, p. 212; Treatment, p. 213; Pathology, p. 218; Geographical distribution, p. 219—Accessory non-toxic goiter, p. 221:—Symptomatology, p. 221; Treatment, p. 222—Malignant goiter, p. 222:—Symptomatology, p. 222; Treatment, p. 222.
Thyroiditis and strumitis, p. 223:—Symptomatology, p. 223; Treatment, p. 224.
Hyperthyroidism, Graves' disease, Basedow's disease, or exophthalmic goiter, p. 225:—Etiology and pathogenesis, p. 225:—Toxemic genesis, p. 225; Psychoneural genesis, p. 227; Predisposing influences, p. 230—Symptomatology, p. 231:—Clinical history, p. 231; Course of the disease, p. 233; Physical findings, p. 234—Diagnosis, p. 239; Complications, p. 241:—Thymus as a complicating factor, p. 241—Treatment, p. 242:—Toxemic group, p. 242; Neurogenic group, p. 246—Pathology, p. 251; Prognosis, p. 253.
Cretinism (infantile myxedema), p. 254:—Etiology and pathogenesis, p. 254; Symptomatology, p. 255; Diagnosis, p. 258; Treatment, p. 259; Pathology, p. 261.
Myxedema or progressive hypothyroidism, p. 261:—Etiology and pathogenesis, p. 261; Symptomatology, p. 262; Treatment, p. 262.
Hypothyroidism or larval myxedema, p. 263:—Etiology and pathogenesis, p. 263; Symptomatology, p. 264; Treatment, p. 265.
Hypoparathyroidia or parathyroid tetany, p. 265:—Etiology and pathogenesis, p. 265; Symptomatology, p. 266; Treatment, p. 267.

Functions of the Thyroid Gland and Parathyroid Glandules.—The diseases of these structures cannot be understood or efficiently treated unless their functions are clearly apprehended. The importance of the thyroid gland to the organism at large is duly emphasized by E. C. Kendall,[1] who recently discovered what may prove to be the active constituent of that organ. He states: "The changes occurring in a patient with thyroid deficiency, or in an experimental animal by the administration of thyroid, are so great that practically every cell within the animal organism is changed. The effects are felt throughout the nervous system and the circulatory system, the rate of metabolism is enormously increased, and even the skin and hair show revolutionary changes. These effects are not produced by ten or a dozen different substances contained in the thyroid secretion; they are produced by a single substance. The function of the gland must be some single chemical reaction which is necessary for the life of the various cells and tissues of the organism."

We need only consider the profound changes which occur when the functions of the organ become impaired, deficient, or abnormally active, to apprehend its far-reaching influence. Exaggerated thyroid activity gradually consumes the tissues as would glowing heat. The victim of advanced Graves' disease only too vividly exemplifies its disastrous effects upon body and mind. Conversely, deficient thyroid activity finds its maximum expression in arrested development, physical and mental; it is so suggestive of automatic vegetative life that Roesch has aptly termed its chief exponent, the *cretin*, a "human plant."

Another function of equal importance asserts itself particularly in the genesis of goiter in all of its forms. The writer, as far back as 1903, urged that we should associate the thyroid gland with, and deem it a part of, *the functions of defence of the body at large, i.e.*, those concerned with immunity—a view since confirmed by the labors of others. He also urged that diphtheria antitoxin owed a part of its virtues to the thyroid secretion. The chimera of strict specificity of all antibodies seemed at the time to overwhelm such a theory, even though based on much evidence. But time has severely shaken the conception of absolute specificity, and, as D. J. Davis[2] wrote recently, referring to vaccines, which, even more than serums, are supposed to embody the very principle of specificity, "the non-specific effect of vaccines is just now probably the most important problem that concerns the vaccinationist. The possibilities of development along this line are many, for the principle concerns an immense number of diseases, both in man and in the lower animals."

The vast experience afforded by the war has likewise tended to efface the rigid lines which for many years captivated laboratory workers. Indeed, while, as stated by J. L. Miller,[3] "clearly-defined, favorable results had been obtained from the intravenous injection of specific vaccines in typhoid, just as good results had been obtained from non-specific vaccines. Much work has pointed strongly to the occurrence of a non-specific factor as the cause. The same results were secured from the intravenous injection of a large variety of non-specific agents, including bacteria, proteins, peptone, deutero-albumose, etc." Obviously, if all these various substances, administered directly into venous channels, can evoke a protective reaction, we must be dealing with some common source, or several coöperative sources of some antitoxic body or bodies, specific only in the sense that it, or they, may embrace within the field of their immunizing action a more or less extensive group of pathogenic substances. Hence the fact that Rupert Farrant,[4] after a comprehensive investigation, concluded, just as the writer had done nine years earlier, that diphtheria antitoxin contained iodin in organic combination, and that this indicated "some close relationship between the thyroid function and the development of certain antitoxins."

The writer's contention was further confirmed independently by the investigations of L. Fassin, of the Bacteriological Institute of Liége, Belgium,[5] who found that the subcutaneous injection of fluid extract of the fresh thyroid gland was "rapidly followed by an increase of alexin in the serum"; of Stepanoff,[6] who ascertained, at the Pasteur Institute, that these defensive opsonins "of the tissue and exudates were, to a considerable extent, the product of the thyroid gland"; of Marbé,[7] also of the Pasteur Institute, who was led to conclude, after comprehensive experiments, that the "opsonic power of the blood-serum increased very clearly after thyroid organotherapy"—more than doubled in one instance—the leukocytes likewise showing a distinct increase of phagocytic activity.

To these experimental facts we may add the older observations of Charrin, Lindemann and others, that animals succumbed more readily to infections after their thyroid glands had been removed, those of Roger and Garnier, Kashimura and others, that infections caused the thyroid to show evidences of marked activity, of Reid Hunt, that thyroid fed to mice rendered them much less susceptible to poisoning by acetonitril, those of Vincent, Frugoni and Grisxconi, Léopold-Lévi and Rothschild and others, that thyroid organotherapy was effective in combating various infectious diseases, including erysipelas and septicemia, of Palmer,[8] that extirpation of the main thyroid body in pigs sufficed to considerably lower their resistance to infection. In view of this testimony we cannot fail to conclude that the thyroid gland takes part in the defensive processes of the body, the activity taking place not in the gland itself—the older detoxicatory theory—but, as the writer has long urged, in the fluids of the body at large, including those in all phagocytic cells.

Special stress is laid upon the rôle of the thyroid gland in general immunity, because, in the opinion of the writer, it underlies and clearly explains most of the disorders of, or general disorders due to, the thyroid with which the general practitioner has to deal. Indeed, it is because most surgeons fail to study with due care this phase of goitrous disorders, including particularly Graves' disease, that they so frequently and, in most instances of the latter disease, unjustly resort to surgical measures, often to the great detriment of the patient. As we shall see, there is no ground for this wholesale utilization of the sacrificial stone; the lines of demarcation between operable and inoperable cases are nowadays clearly defined. If enough trouble is taken to trace the glandular disorder to its source, and if the case, when first seen, is not allowed *by the general practitioner* to drift until an overworked organ is more or less converted into an area of fibrous or other degenerative tissues, which the surgeon alone can eliminate, the knife will lose its unmerited empire.

How does the thyroid gland carry out these important functions?

Iodin in organic combination has shown itself to be the main active constituent of the thyroid secretion ever since Baumann in 1885 discovered a compound containing this halogen in what he deemed the glandular product, which he termed "iodothyrin." Oswald, however, subsequently identified the product as an iodized globulin, thus more closely associating its functions with those of the blood. In 1907, the writer of this article stated that iodophil leukocytes supplied the thyroid gland (and parathyroids) with a ferment-like compound of iodin, which on reaching the lungs was absorbed by the red-corpuscles and was by them distributed to all tissues.

The most recent contribution in this direction is that already referred to, *viz.*, that of E. C. Kendall, of the Mayo Clinic. This physiological chemist isolated from the gland, in the course of an extended and careful investigation, a crystalline substance containing no less than 60 per cent. of iodin and possessing the physiologic activity of the gland itself. Preliminary work directed toward a determination of the structural formula of this substance—termed by Kendall the "alpha iodin compound of the thyroid" and identified subsequently as "thyroxin"—made it appear[9] to be carbonic acid in which one of the hydrogen atoms is replaced by di-iodo-indol.

The absorption of iodin by the thyroid, and its elaboration into the thyroid hormone, have been subjects of experimental studies by David Marine and his co-workers. Marine[10] observed that living thyroid tissue has an extremely pronounced affinity for iodin, which is rapidly taken up by the gland in whatever form and by whatever method it is administered. The amount of iodin absorbed was found to vary not only according to the size of the gland but also according to the existing degree of thyroid hyperplasia and the degree of saturation of the thyroid with iodin at the time. The colloid of the organ is not the source of thyroxin. With J. N. Rogoff,[11] the same experimenter found that while the storage of iodin in the thyroid from potassium iodid is practically instantaneous, transformation into the specific hormone is much slower, only a small fraction of the iodin taken up having been thus transformed after thirty hours.

The mode of action of thyroxin appears to be, according to Kendall, "to furnish the animal organism with ammonia resulting from the deaminization of amino-acids. The amino-group in amino-acids is unavailable for the formation of urea and other nitrogenous compounds until it has been split out of the amino-acids. This deaminization appears to be the function of the thyroid." While this action, based upon test-tube analysis alone, may play some rôle in the metabolic processes which, as we have seen, the thyroid gland so profoundly influences, it fails to account for various phenomena of capital interest to the clinician. How, for instance, does it explain the striking increase in the absorption of oxygen, varying from 20 to 75 per cent., observed by Beebe[12] and others, when the thyroid gland is administered in cases of myxedema or cretinism, or the fact that thyroid feeding will cause an increase of from 10 to 40 per cent. of the oxygen intake in normal animals? How does it explain the familiar increased elimination of phosphoric acid first observed by Chittenden in 1897, and that of phosphates, which follows feeding thyroid to normal animals, and the marked decrease in the case of animals from which the thyroid gland has been removed? Again, how does it account for the familiar rapid reduction of fat in obese subjects which thyroid gland may cause, and which, as emphasized by Schöndorff,[13] will exhaust all reserve fats before the nitrogenous tissues—which alone would be influenced by thyroid if Kendall's view is right—are affected at all? What explanation does it furnish of the influence of the thyroid, and thyroid feeding, on the immunizing processes to which we have referred? These are only a few of the many facts, familiar to clinicians, which Kendall's conception fails to explain.

This does not apply, however, to the conception of the function of the thyroid (working in conjunction with the parathyroids) advanced by the writer of the present article in 1907. Briefly, this theory is that the thyroid product, a compound rich in iodin, stimulates oxidation by increasing, as a ferment, the vulnerability of the phosphorus, which all cells, particularly their nuclei—including those of fat-cells—contain, to oxidation by the oxygen of the blood. Furthermore, this process, by applying as well to bacteria—the ash of which is largely phosphoric acid—and to toxins, upon which it acts as sensitizing substance or opsonin, thus favors their conversion into eliminable wastes by antibodies. This view alone explains the laboratory phenomena observed in practice, including the excretion of phosphates, the intense oxidation, both phases of metabolism, the stimulation of the autodefensive processes, including phagocytic activity, the fact that thyroid feeding provokes, or, conversely, that thyroidectomy or thyroid insufficiency inhibits all these functional phenomena. It has therefore been adopted as the basis of the analysis of the diseases of the thyroid gland and their treatment submitted in these pages.

However, inasmuch as Kendall's thyroxin has been found in as small a dose as 1/6 grain (10 mg.) to increase the metabolic rate in myxedema and cretinism, and to produce symptoms of exophthalmic goiter when given in excess, it bids fair not only to take the lead over all glandular active agents so far isolated, but to furnish in the near future a logical basis for all processes, physiological and pathological, concerning the gland, the chemical reaction so far submitted by Kendall being admittedly theoretical.

Before we can proceed with our review of the diseases of the thyroid, it is necessary to refer to a set of organs which virtually form part of the thyroid mechanism, although structurally separated from it.

Functions of the Parathyroids.—Formerly, the thyroid alone was taken into account in all physiological and pathological problems. In 1880, however, the two external parathyroids were discovered by a Swedish investigator, Sanstrom, while in 1893, the two internal parathyroids were discovered by Nicolas of Nancy, France. These four small organs, each the size of a small pea, were found by Gley, of Paris, to have physiological functions which tended to show a connection with those of the thyroid proper, a fact which has caused some investigators to adopt as an expression of the associated functions the term "thyroparathyroid apparatus." We shall see presently that there is good ground for this position, in the light of available data.

Although, as stated above, four parathyroid glandules are normally present, some cadavers, even after careful sections of the thyroid, show but three or even two of these small organs. The two superior parathyroids generally lie behind the middle third of the thyroid proper, opposite the lower border of the cricoid cartilage, while the inferior are located behind the lower third of the thyroid. At times an inferior parathyroid is situated at or even below the lower pole of the thyroid. Only rarely is a parathyroid embedded in the thyroid tissue proper; as a rule, each is surrounded by fibers of the thyroid capsule, and clings to the latter when it is stripped from the thyroid. Hence the fact that surgeons carefully leave the thyroid capsule when any part of the organ is removed. Small supernumerary parathyroids have occasionally been noted, generally below the thyroid, or within the thymus or the thyroid itself.

Structurally a parathyroid glandule is composed of compact epithelial cells, embedded in a reticular stroma. Occasionally these epithelial cells are formed into lobules, each of which contains a central lumen filled with colloid. The cells are divided into two types, the more numerous or principal epithelial cells, and the oxyphil or granular cells. The parathyroids differ from the thyroid gland proper, according to Beebe,[14] in that the former contain chiefly nucleoproteid; the thyroid contains an especially large amount of globulin.

The thyroid and parathyroids are related through their vascular supply. The arterial vessels of the parathyroids are derived chiefly from the inferior thyroid arteries and in part from the superior thyroid arteries. Anastomoses may also bring blood from the tracheal, esophageal, and pharyngeal vessels. The existence of nerve-fibers ending in immediate relationship with the vessels leading to the parathyroids has been shown by Rhinehart. They form part of the sympathetic system.

An important distinction between the thyroid proper and the parathyroids asserts itself when the physiological characteristics of the two organs are compared. We have seen that the thyroid, through its secretion, influences general metabolism very actively. When, therefore, this organ is entirely removed, the parathyroids being left intact, the postoperative phenomena witnessed are those of slowed metabolism with cretinism or infantile myxedema in the young, and true myxedema (*vide infra*) in the adult as an ultimate result. In other words, the postoperative life is prolonged. When, however, the parathyroids are removed, very different phenomena appear, *viz.*, the symptoms are essentially nervous, and death ensues rapidly. The morbid effects are those of tetany, characterized especially by a tendency to spasms, usually beginning about twenty-four hours after the removal of all the parathyroids; death generally follows in from three to five days. In dogs a single parathyroid suffices in most instances to obviate tetany, but in some animals the removal of even two parathyroids out of four has been observed to induce the spastic state.

Many observers, including the writer, regard the parathyroids as coöperating with the thyroid, thus constituting, as previously stated, the thyroparathyroid apparatus. But others believe that their functions are independent, as the foregoing symptomatology following the removal of either organ independently would suggest. Various facts, however, tend to show that the independence of the two organs is not as complete as might be supposed. Thus, some evidence has been collected to the effect that after thyroidectomy the parathyroids may assume to some degree the functions of the thyroid. As shown by Vassale, however, the injection of thyroid extract is capable, like that of parathyroid extract, of allaying the convulsive disorders which follow complete parathyroidectomy. According to Edmunds, extirpation of the parathyroids causes hypertrophic histological changes in the thyroid. Vassale and Generali[15] found that after death from parathyroidectomy the thyroid contains no colloid, thus suggesting that the formation of the thyroid product is in some way related to the functions of the parathyroids. In experiments performed by Gley[16] an apparently complete parathyroidectomy, with partial thyroidectomy, did not prove fatal until the remaining lobe of the thyroid was likewise removed. It has been found, moreover, that pure thyroid tissue, when grafted, can assume the functions of both thyroid and parathyroids and thus prevent the tetany due to parathyroidectomy, and the resulting death.

Of great practical importance to the general practitioner is the fact that meat will cause enlargement of the thyroid, at least in certain animals. Tanberg[17] found that if two or more parathyroids were removed from such animals, this enlargement failed to appear. He also noted that an existing enlargement of the thyroid due to a meat diet disappeared when a sufficient number of parathyroids had been removed. Again, we have seen that removal of the thyroid caused a lowering of the body temperature. The same phenomenon was observed by Jeandelize[18] after the removal of the parathyroids.

The writer, we have seen, has attributed to the thyroparathyroid apparatus an important rôle in the immunizing function of the body at large. The fact that removal of the parathyroids causes tetany has been attributed by him to an accumulation of toxic wastes in the blood capable, like strychnin, of irritating the central nervous system, thus strongly suggesting a capacity on the part of the parathyroids to destroy or prevent the morbid action of certain spasmogenic wastes or poisons. Further evidence in favor of such a conception is afforded by the fact that the blood and urine of parathyroidectomized dogs have been found by Rogowitsch and others to cause convulsions in normal animals. This is further controlled by the fact that parathyroid extract, when fresh, will at least temporarily arrest the convulsive phenomena following the removal of the parathyroids. Finally, according to Kendall,[19] who, we have seen, has advanced the hypothesis that the function of the thyroid is to regulate the deaminization of amino-acids, the parathyroid function is to detoxicate the ammonium carbonate formed by union of the removed amino-group with the carbon dioxid in the blood. He states that, according to the results of previous investigators, it seems probable that ammonium carbonate is responsible for the tetany following parathyroidectomy. On the whole, Gley's conception of a functional relationship between the thyroid and parathyroids stands on a sound foundation.

Another elucidative fact of practical importance is the possible relationship between the thyroid functions and the calcium supply. MacCallum and Voegtlin[20] found that calcium salts arrested tetany due to parathyroidectomy, and they ascribed the antitoxic action of the parathyroids to some influence which they exerted upon calcium metabolism. This question will be further taken up under the heading of Parathyroid Insufficiency (p. 265).

GOITER (STRUMA, BRONCHOCELE)

Definition.—This term, although applied as a rule to enlargement of the thyroid gland, causing a more or less prominent swelling in the anterior portion of the neck, is also used to denote enlargement of thyroid tissue elsewhere, at the base of the tongue, for instance, where enlargement of the thyroglossal duct may form a tumor, termed for that reason *lingual goiter*. Supernumerary thyroids found in various parts of the body are known as *aberrant goiters*. An enlarged thyroid through which a large blood-vessel passes anomalously is termed a *perivascular goiter*, while a projection of an irregularly enlarged thyroid behind a large vascular trunk is identified as a *retrovascular goiter*. Finally, such a projection may tend downward and grow behind the sternum, forming the severe type known as retrosternal goiter. Besides these various forms there are the various histological types, the exophthalmic, colloid, cystic, etc. Goiter, as here considered, is the essential expression of enlargement of the thyroid as a local phenomenon and without systemic symptoms. In this sense it should be clearly differentiated from the conditions to which some of its forms may lead, namely, hyperthyroidism, or its more dangerous manifestation, exophthalmic goiter, or Graves' disease, which are attended by more or less marked evidences of intoxication by thyroid and other products, and which will be considered under separate headings.

Etiology and Pathogenesis.—The cardinal feature of modern research is that goiter, wherever it occurs, can be produced by a number of different toxic agents. The *drinking water* in many goitrous districts is known to underlie its pathogenesis, the residuum of filtered water from certain fountains in Switzerland having been found, when added to harmless water, to convey to it goiter-producing properties. Again, *limestone* districts show a large proportion of goitrous inhabitants. According to Kocher, however, "goiter water differs from goiter-free water in containing many more microörganisms." Here probably lies the secret of the vast majority of cases of endemic goiter. McCarrison and others have recently afforded strong support to the bacteriogenic view of goiter. Animals allowed by this observer to drink only water contaminated with feces very readily developed goiter, while soil deposits on the sides and bottom of water-channels, tanks, wells, etc., were found to be capable of contaminating the contained water. In the opinion of the writer of the present article, the habit of fertilizing the soil with human feces, so common in Switzerland, undoubtedly accounts for much of the prevalence of goiter in that country. Hence the fact that it occurs mainly in valleys of mountainous districts in all countries where contaminated waters tend to accumulate. The participation of *calcium* in the etiology has been explained on the ground that it affords, in the soil, a favorable medium for the pathogenic microörganisms, the toxins of which are the active poisons in the process. Bacterial infection from the tonsils may undoubtedly, as demonstrated in the writer's clinical experience, also provoke goiter, as may also infection from the teeth and gums, the nasopharynx and many other locations.

Mountainous regions are generally regarded as favorable to the formation of goiter foci, but this is probably due to the fact that the declivities favor the accumulation in the valleys of excrementitious materials contaminating the mountain sides. Thus, as stated by Hunziker,[21] there are years during which a greater number of goiter cases develop than in other years, a fact which he tentatively attributes to the washing away from the soil of salts containing iodin. But a clearer explanation is afforded by the washing down to the lower levels, valleys, etc., where goiter is known to prevail, of the fecal matter known to produce it. Indeed, Susuki caused goiter in rats by feeding them with rice contaminated with rat feces and also by injecting subcutaneously a solution of the latter. The prevalence of goiter among people of filthy habits, such as the peasants of Bosnia, who pick their food out of a common bowl with their fingers—doubtless the same which they use for toilet purposes—thus finds its explanation without necessitating Kutschera's so-called "contact theory."

McCarrison has likewise caused goiter in animals by giving them water polluted with *feces.* In a more recent series of experimental studies in goats[22] he also found that congenital goiter was due to the action on the fetal thyroid gland of toxic substances from the maternal intestine, originating through food and water from microörganisms, derived in turn from fecally-contaminated soil. That some pathogenic organisms or their toxins might act as the exciting cause had previously been urged by many investigators, including Poncet, Jaboulay and Rivière, Klebs, Kocher, Lustig and Carle and others. McCarrison believes that the *contagium vivum* of goiter exists in greatest abundance in the soil of contaminated localities, and that it requires a calcareous soil to enable it to flourish. We have seen that calcareous waters favor bacterial growth. That we are dealing with some organism or organic agent and not with a mineral is well shown by the fact that, in the case of an entire family of 9, observed by Breitner[23] goiters were visibly diminished at the end of four weeks, merely by boiling all waters used internally. There was an immediate recurrence when the use of unboiled water was resumed.

Evidence accumulated from many directions tends to show, however, that no special organism need be considered as sole exciting cause, but that various types, including prominently the *Bacillus coli,* pyogenic bacteria, including staphylococci as shown by Halsted, and various parasites, may likewise act as causes, the *Entameba buccalis* particularly being a cause of tonsillitis, as suggested by Evans, Middleton and Allen J. Smith. The writer has seen goiters disappear spontaneously after tonsillar or peridental abscesses had been eliminated. This applies likewise to pyogenic disease of the nasal cavities and sinuses. That toxins may act as causes is well shown by the observations of Farrant that marked enlargement of the gland results from injections of diphtheria toxin into guinea pigs. Finally, temporary goiter is well known to occur under the influence of many infectious diseases, especially typhoid fever, diphtheria, scarlatina, measles, parotitis, erysipelas, pneumonia, pertussis, dysentery, rheumatic fever, puerperal fever, syphilis and influenza.

Another phase of the process of intoxication is the goitrous enlargement often witnessed during *pregnancy.* It is so frequently observed in some parts of Italy that it is popularly regarded as an early sign of the pregnant state. In the United States, the proportion of discernible glandular enlargement is probably far smaller; that noted by Markoe in New York,[24] *i. e.,* 132 instances in 1,586 pregnancies, representing probably the normal average in non-goitrous districts. In countries where goiter is endemic, however, the proportion is probably much larger. No explanation other than that afforded by the writer many years ago has been vouchsafed so far, and his view may be said to impose itself as the correct one when the antitoxic functions attributed to the thyroid in the foregoing pages are taken into account. Briefly, Markoe's view is that toxic wastes and detritus, those of the fetus added to those of the mother, impose upon her thyroid gland a degree of functional activity which it is unable to carry out, either through inherited or acquired insufficiency. The gland may be equal to the normal needs of the individual, and yet not react to the abnormal demands without excessive activity or hyperthyroidism, sufficient to cause enlargement, *i. e.,* goiter, through excessive hyperemia of the gland. That this enlargement is purely compensatory in practically all cases is shown by the fact that out of 132 pregnancy goiters observed by Markoe in his obstetric practice, only 8 proved toxic. The increased functional activity thus has a physiological purpose, that of increasing the antitoxic power of the system at large. The organ then resumes its normal activity when the need of abnormal functioning is eliminated by the birth of the child.

The influence of *heredity* is seldom manifest in cases observed in this country, as compared with its important rôle in Switzerland, where endemic foci are numerous and where many generations of sufferers have succeeded one another. It should nevertheless be borne in mind when therapeutic measures are to be inaugurated, since it has seemed to the author to delay recovery to a marked extent. This fact shows the need for prudence when a prognosis is to be expressed. Not only is the deteriorating influence of the pathogenic agent exercised upon the organ generation after generation, if the individuals persist in residing in a goiterogenous district, but all other ductless glands, by losing to an increasing degree the stimulation which the thyroid hormone affords, likewise become insufficient. The newborn child thus inherits a tendency not only toward partial inactivity of the thyroid gland but also toward partial or complete functional insufficiency of the adrenals, thymus, pituitary, etc. As the child is also subjected to pathogenic conditions after birth, a cumulative deterioration occurs which imprints itself upon the whole physique and mentality of the individual. The facies of these unfortunates in certain districts of Switzerland is typical in its ugliness. The skin acquires a yellowish, dirty color; the osseous structure plainly shows inhibited development, while the mentality gradually declines with succeeding generations until cretinism appears—sometimes as early as the third generation. Children and women, in the order given, show greater predisposition to the development of goiter than do men.

Unfortunately, migration to non-goitrous districts does not always protect the offspring, particularly on the maternal side; nor does it even protect the grandchildren in every instance, as endocrinological case records well show. It is important to bear this in mind, for the defensive functions in these cases are below normal. Women thus affected readily yield to infection, and are apt to show puerperal eclampsia unless thyroid gland in appropriate doses is administered to them during pregnancy. The offspring are also subject to the development of goiter, under conditions of intoxication which would not affect unpredisposed persons. This has been frequently illustrated in the writer's own practice. Deaf-mutism is another condition which goiter entails. Goyanes[25] refers to a family in which two of the daughters of a goitrous woman were deaf-mutes. He reports cases of deaf-mutes with goiter, and also of deaf-mute cretins, the antecedents of which always showed goiter in both parents or in the grandparents.

This dark picture is mitigated, however, by many exceptions. A large number of instances have been recorded in which a goitrous mother removed to a non-goitrous district gave birth to a non-goitrous and intelligent child, whereas, as is well known, such a mother living in an endemic district may bear a cretin. Even a cretinous mother has been known to bear a non-cretinous child if, during her pregnancy, she is removed and kept entirely away from contaminated territory. Moreover, the permanent removal of goitrous families from contaminated districts has been so effective in many instances as to have warranted the conclusion on the part of several reliable observers that the hereditary taint disappeared totally after the second generation. If to this we add the aid available through the administration of iodin in minute doses in such families, a hopeful view on behalf of these subjects may certainly be entertained.

Adolescence, particularly in girls, seems to predispose, not necessarily to goiter, but to enlargement of the thyroid. This applies not only to regions in which true goiter is endemic, but also to those which are free from any such influence. In fact, if any aggregate of young girls in so-called goiter-free districts is cursorily examined, the region of the thyroid will be seen in many cases to bulge more or less prominently and to assume in some the proportions of a goiter. These goiters are usually atoxic. In rare cases in the writer's experience, one of the toxic type has been found to appear, the tachycardia fluctuating from 120 to 140. In the atoxic type, a deficiency of iodin prevails in some cases, for the use of this halogen in small doses, in the form of the iodids, or thyroid gland, soon slows the pulse and causes the goiter to recede. In such cases the gland is simply unable to obtain from the average food ingested the proportion of iodin required to enable it to carry on its antitoxic functions, and it functionates inordinately, enlarging while doing so in its attempt to meet the physiological needs. Even a stay at the seashore sometimes suffices to supply the slight proportion of iodin required to restore the functional equilibrium.

Some adolescents do not respond to this virtual iodin test; the halogen may, in fact, arouse toxic phenomena in these cases, even when given in minute doses. In such instances the underlying pathogenic influence is not a deficiency of iodin but a toxemia. As previously stated, the writer has obtained complete and relatively rapid disappearance of the goiter after the removal of diseased tonsils, and also after the extraction or successful treatment of abscessed teeth. But in the majority of instances, the intestinal canal is the source of the pathogenic agent or toxins. McCarrison has incriminated some undetermined variety of colon bacillus, or perhaps ameba, but the many pathogenic factors suggested by a corresponding number of infections capable of evoking goiter tend to indicate clearly that a specific organism is not needed to explain the production of the disease. Briefly, in endemic foci there is good reason to believe that a common toxin of fecal origin is the principal cause. This view is supported by the large proportion of cases in some districts, for instance, 80 per cent. in a school at Lunde, Norway, referred to by Kjolstad.[26] In all localities, however, which are not endemic foci, we must seek for other sources of infection, focal or general, to explain the defensive reaction on the part of the thyroid sufficient to produce its enlargement, *i.e.*, goiter. If long-continued, enlargement may induce pathological changes in the organ which render this overgrowth not only permanent, but also, in a large proportion of instances, dangerous to life.

Symptomatology.—The first symptoms observed may be a slight fullness of the front of the neck, when the whole gland enlarges evenly, or the presence of a shallow lobule or prominence when the isthmus of the thyroid is first involved, or a slight fullness on either side of the middle line filling the hollow between it and the border of the sternocleidomastoid muscle, when one lobe or the other begins to enlarge, or again, the unusual tightness of collars previously worn with comfort.

In the goiter of adolescents, especially of young girls, and particularly during the menstrual period, this sensation of tightness about the neck is sometimes experienced irrespective of any neckwear, owing to the pressure of the enlarged gland on the trachea. This suffices at times to cause dyspnea, cough, headache, vertigo and restless sleep disturbed by unpleasant dreams.

Early pressure symptoms usually occur, however, after the goiter has shown itself externally, and when the skin and subcutaneous structures are beginning to offer resistance. If they appear very early without external manifestations, substernal goiter should be suspected, the sternum offering a firm anterior wall to force the growth posteriorly. Again, pressure symptoms vary with the shape of the goiter; when it is soft and evenly diffused over the trachea, pressure is not as likely to occur as it is when it is located on one side and tends to be hard, as is often the case in endemic growth, owing to the dense colloid. We shall see that the late pressure symptoms are far more severe than the foregoing.

A thyroid growth is characteristic in that it follows the movements of the gland during deep respiration, deglutition and coughing, owing to the fact that its connection with the cricoid cartilage causes it to follow the movements of the larynx. When the patient throws his head backward and swallows or coughs, the whole mass, if it is a goiter or other thyroid tumor, moves up and down with the larynx. The only exceptions to this rule are: when the size of the mass is excessive, when a malignant growth or an inflammatory process produces adhesions which inhibit the vertical movements, or when the patient has received *x*-ray treatment, which also produces adhesions. But under any of these conditions, the growth is so obvious that differential diagnosis to determine its character is alone in order.

Palpation is useful in determining the same connection with the laryngeal motions, the enlarged gland slipping upward under the palpating fingers when the head is thrown backward and the patient is asked to swallow or cough. The outline of the growth may also be determined by palpation, but this requires the bending forward of the head to relax all the neighboring muscles and the structures overlying the goiter. The tips of the fingers can then, by sufficient pressure, be made to follow the sulcus formed by the edge of the goiter. If this is deftly done, some surprising vagaries of shape are often discovered, including at times a substernal projection capable of causing severe symptoms, dyspnea in particular, even though the goitrous projection above is very shallow. The percussion note over the upper part of the manubrium sterni will be found to be dull, thus suggesting the presence of a retrosternal projection. *X*-ray examination may then be used to confirm the diagnosis.

Auscultation, particularly with the stethoscope lightly placed over the enlarged gland or near its upper edge, serves to identify the cause of dyspnea, if there is any, by revealing a tubular, sometimes rough, sound most marked on respiration. The location of the pressure may sometimes be discerned with the laryngoscope. With the aid of a stethoscope, murmurs may also be heard in the dilated blood-vessels of the gland, while the growth itself may be seen to pulsate, when observed from the side.

We shall see below, under Pressure Symptoms, that as the goiter develops either in size or in character, complications occur which render even these non-toxic goiters dangerous to life.

NON-TOXIC GOITER

Types and Prognosis.—Recognition of the nature of the goiter observed is closely connected with the kind of treatment to be adopted. It is therefore of prime importance to bear in mind the characteristics of each type.

NON-TOXIC PARENCHYMATOUS GOITER.—The first in order is the non-toxic parenchymatous goiter. This type, also termed "non-symptomatic," "simple" goiter in the foregoing pages, gives rise to no general symptoms *per se;* what discomfort it produces is due to pressure upon neighboring structures or to the insinuation of some part of it between them. The latter complication is rare; in most cases, particularly in adolescents and young subjects, the gland is simply enlarged slightly, more so on one side than on the other, and is more or less compressible. The patient, usually of the female sex, generally applies for treatment with the object of ridding herself of an unsightly deformity. In most of these instances, when the condition is not due to pregnancy, it is the result of water-borne organic, probably focal, infection, *i.e.,* of some toxemia of dental, tonsillar, intestinal, etc., origin which the thyroid is unable to meet adequately without inordinate functional effort. When the cause of the toxemia is removed and appropriate compensatory and local treatment resorted to, the prognosis of these growths is, as a rule, favorable if seen comparatively early, *i.e.,* before structural changes have occurred.

Hypothyroid Goiter.—These goiters may, however, be of the hypothyroid type. In these subjects the gland, notwithstanding its enlargement, cannot meet the needs of the organism, either those involved in combating infections, or those of metabolism. In the child, this constitutes a step toward cretinism, a frequently observed association in endemic centers. In sporadic cases, however, hypothyroidism results when areas of fibrosis are formed, following hemorrhages in the parenchyma in the course of one or more infectious diseases. It may also be hereditary, the child developing to a more or less marked degree into a "backward child," physically and mentally. If such a case is examined carefully these symptoms of hypothyroidism will become apparent. Hypothermia is the rule, with cold feet and clammy hands. Bradycardia is usual, the pulse sometimes ranging considerably below sixty beats. There is a marked tendency toward hyperidrosis, especially of the feet, excessive general sweating occurring on the least exertion and sometimes without it. The patient may complain of rheumatic pains, particularly in the occipital region, which are most marked before rising. The urea excretion is more or less reduced, usually about one-third. Myxedema or cretinism in the child may supervene as the fibrous degeneration of the organ proceeds. This form is also amenable to appropriate medical treatment.

It is important to differentiate non-toxic diffuse goiter from toxic non-exophthalmic goiter, which is only a larval form of Graves' disease, and is characterized by tachycardia, tremor, and other symptoms of the latter disorder in severe cases, and the treatment of which differs totally from that of the non-toxic goiters.

NON-TOXIC NODULAR GOITER.—On the whole, nodular goiters are characterized by an irregular development of abnormal areas, and differ from the diffuse goiters, in which all parts of the organ are enlarged to a more or less marked degree, with a tendency toward regeneration.

The *colloid goiter* is the most common of the nodular goiters. It is irregular in shape, the surface being uneven or bosselated, owing to the presence of masses of tenacious colloid varying in size, which fill and expand the follicles, lymph-spaces, and even the whole organ in some instances. It is usually quite hard and resistant, and does not yield under pressure of the hand, the colloid failing to flow into neighboring cavities, as is sometimes the case with softer goiters. The nodular irregularity is usually more marked in one lobe than in the other; the hardness also varies, being resistant in places and softer in others. Colloid goiters are not influenced by internal medication.

True *fibrous goiters,* due in most instances to inflammation of the thyroid or to hemorrhagic foci in the course of infectious diseases, are also hard, but differ from the former in that they are not lobulated but hard throughout. As a rule they are small, the process suggesting sclerosis with its resulting contraction. As this process entails more or less compression of the glandular elements, their functions may become increasingly inhibited, and the case lapses into one of cretinism if in a child, or one of myxedema if in an adult. Such goiters sometimes, although very rarely, become as hard as wood, and for this reason the condition has been termed *ligneous goiter,* or *Riegel's disease.* It may develop rapidly as the result of local inflammatory changes, and soon produces dyspnea, stridor, and dysphonia due to compression of surrounding structures. It may also be followed by myxedema.

The *cystic goiter* is another form occasionally met with. It is usually soft, smooth and globular, and may even fluctuate. It may develop from a colloid goiter or from an adenomatous goiter in which the glandular epithelium is embryonic and produces but little colloid. It may consist of retention cysts or of hemorrhagic cysts due to rupture of one or more dilated blood-vessels into the glandular parenchyma.

As a rule, the dangerous *intrathoracic goiter* also belongs to the non-toxic type. It develops from either horn of the gland and passes downward behind the suprasternal notch into the thorax, aided by the downward movements of the thyroid and the suction exerted upon the projection when the chest expands during inspiration. Short-necked individuals and those whose occupation causes them to keep the head bent forward during prolonged periods each day are those most exposed to this variety of goiter. As it grows the symptoms of compression become increasingly severe. The history of the growth, the severity of the symptoms, and an x-ray examination soon establish its identity.

The form met with in the *newborn,* and *congenital goiter,* are more frequently observed than is generally believed. The goiter may be purely congestive, the result probably of continued pressure, either during face presentations or by forceps, in the course of parturition; or it may be due to persistence of fetal circulation. In most instances, however, it is of the inherited form previously described, *i. e.,* a congenital goiter, the mother being goitrous. The goiter is usually of the parenchymatous type, but often develops in such a way as to encircle the trachea sufficiently to inhibit respiration—the "constrictive goiter" mentioned by French authors. In some instances, it encircles the esophagus. Death may follow a few respiratory efforts, or occur suddenly after ligation of the cord.

If the child lives, dyspnea with hoarseness in crying, and cyanosis, are salient symptoms, and also, if the esophagus is involved, dysphagia, the infant refusing to nurse. A slight swelling in front of the neck may be observed, particularly if the head is thrown back. In true pressure cases, the symptoms, with perhaps screaming and writhing, may disappear within twenty-four hours; in most instances, however, they recur intermittently.

Pressure Symptoms.—Pressure symptoms of a serious type occur when the goiter has grown in such a way as to interfere with the functions of neighboring structures. The slight dyspnea previously referred to, occurring mainly on exertion, may assume severe proportions when, as in the case of nodular goiters, the trachea is compressed or distorted by the pressure of either lobe, causing "goiter asthma." This may assume the proportions of orthopnea with more or less stridor, a loud whistling noise being heard during both inspiration and expiration. It is often accompanied by cyanosis. The mass need not necessarily be large to produce dangerous symptoms; moreover, any condition capable of causing an inflammatory swelling of such a goiter, or a hemorrhage in its parenchyma, such as an infection, a blow, a fall, violently bending the head on the thorax, etc., may cause sudden death from asphyxia.

Pressure on the blood-vessels of the neck, by disturbing the circulation and interfering with the equable return of the blood to the heart and lungs, may also cause cyanosis, which then becomes especially marked about the lips, cheeks, tongue, etc., particularly during exertion. The interference with the cerebral circulation may also produce headache, vertigo, and other signs of congestion. Edema through venous compression is sometimes observed.

Pressure on nerves occurs frequently, particularly in nodular goiters with hard, but not necessarily large, lobes. If the pressure is on the recurrent laryngeal nerve, partial or complete paralysis of one or both vocal cords may result; unilateral paralysis, however, usually occurs on the right side. Recovery results after removal of the goiter if the pressure has not lasted too long. The patient seldom recovers from prolonged pressure paralysis. Numbness of the fingers and arm, and sometimes paralysis, occurs when a large growth compresses or causes traction of the brachial plexus.

Hoarseness may also be caused by pressure upon the recurrent laryngeal nerve, but in most instances it is due to a chronic catarrhal process of the laryngotracheal mucous membrane, resulting from the pressure of the goiter on the trachea and from interference with the functions of its epithelium, which keeps the tracheal mucosa free from foreign substances, mucus, etc. It is sometimes due to direct infection through defective secretion of the tracheal mucus.

NON-TOXIC GOITER HEART.—Dilatation of the heart, particularly in advanced cases and in aged subjects, is not infrequent in non-toxic goiter. It is mainly due to the interference with the respiratory mechanism and to pressure on the blood-vessels of the neck. It may also contribute toward the dyspnea referred to above and to the various other symptoms mentioned, vertigo in particular, and give rise to phenomena of defective compensation, notably in advanced cases, when it causes epistaxis and edema. While at first mitral insufficiency may appear, this is ultimately followed by other valvular murmurs, and finally by tachycardia and feeble contraction, arhythmia and terminal symptoms, if the case is neglected. Advanced cardiac symptoms of goitrous origin do not yield readily to treatment.

Treatment.—PROPHYLAXIS.—The foregoing as to the curability of non-toxic goiter, when treated early, is substantiated by the recent observation of Kimball and Marine[27] that one-third of 141 cases of uncomplicated simple goiter disappeared after the use of **sodium iodid** in relatively small doses. This may be given internally, without danger of producing toxic symptoms other than perhaps an iodid rash, which disappears on cessation of the treatment. In the study of 4,466 school girls in the Great Lakes district previously referred to, the same authors[28] gave experimentally either **syrup of hydriodic acid** or **syrup of ferrous iodid** in 15 minim (0.92 c.c.) doses daily for two or three weeks, repeating the course twice yearly. Ultimately they selected sodium iodid, given in 3 grain (0.195 gram) doses each school day, ten times, to pupils in the fifth to eighth grade inclusively, and 4 grain (0.26 gram) doses daily, fifteen times, to pupils in the ninth to twelfth grade inclusively, these amounts being repeated twice annually about the first of May and of December, and administered at the school by the teachers or nurse. Roux,[29] emphasizing also the "marvellous and rapid action" of preparations of iodin in minute doses on diffuse parenchymatous goiters of young children and animals, recommended that a few crystals of iodin be placed in each schoolroom and renewed as fast as evaporated, to replace the seashore iodin so helpful in such cases.

The regional absence of iodin in goitrous districts has been emphasized by Hunziker.[30] In one comparatively goiter-free canton of Switzerland he found that the cooking-salt, *i. e.*, sea-salt, had an unusually high iodin content. The iodin supply of the thyroid being derived from the food, he recommends that iodin-containing manure be used as fertilizing material where goiter is endemic, in order that the vegetables consumed may contain the needed iodin. This might have the added advantage, as far as Switzerland is concerned, of replacing the human fecal material which, in the author's opinion, plays so important a rôle in that country in perpetuating goiter.

Boiling the water used has been found to be very efficacious as a prophylactic measure. Flowing water has also proven less harmful than stagnant water. **Ultraviolet rays** and **sunlight** also tend to purify suspected waters. Bernhard,[31] in favoring sunlight, calls attention to the fact that dwellers on well-sunned slopes and mountain valleys are far more robust than shade-dwellers—a fact which experience elsewhere in the realm of physical therapeutics has abundantly confirmed.

To the endocrinologist the statement so often quoted by patients, and credited to their family physician, that "surgical removal is the only cure for goiter" appears, stated mildly, reprehensible. In many instances the dread of an operation causes more or less prolonged delay in applying for relief, and when the patients finally come for advice, many have stepped beyond the threshold of safety. In other words, they have given the goiter time to undergo histological changes which nothing but the knife can remove. Basing his opinion upon considerable experience, the writer does not hesitate to submit as an axiom, that *any true goiter may be treated successfully during its earlier stages without surgical intervention,* provided the prevailing empiricism is replaced by an intelligent inquiry into the cause of the goiter, and provided the functions of the gland are taken into account as factors in the morbid process.

If any doubt exists concerning the disappearance of goiters under appropriate conditions, one has only to consider the seemingly automatic recoveries which ensue when goitrous individuals are **removed from endemic districts.** Crotti, for instance, in his recent work,[32] states that "according to Guyon, emigrants from the Canton of Valais lost their goiters in Algiers; and Hübner reports that 16,000 emigrants from the district of Salzburg, in general goitrous, saw this infirmity disappear after settling in Prussia." Obviously, surgical removal is not "the only cure for goiter."

Following out the analytical process we are brought to ask *why* did the goiters disappear in the multitude of cases referred to? It is self-evident that it was due to the elimination of the toxic substance, whatever that might be, from the only common agent used by these goitrous thousands—water used as a beverage, for cooking purposes, etc. Yet, while this applies to the endemic form of the condition, many sporadic cases have shown that removal of fecal stases, diseased tonsils, abscessed teeth, and other sources of toxemia, have caused complete disappearance of goiters. We are, therefore, not dealing with a specific cause but with *several,* probably *many,* toxic agents capable of causing goiter. As McCarrison states,[33] referring to the writer's researches, "Sajous showed in 1902 that the injection of various bacterial toxins into man and the lower animals excited more or less actively, according to their virulence, the thyroid gland's functional activity"—the latter including, as we have seen, participation in the immunizing functions. This fact, with McCarrison's own conclusion (1910-13), previously referred to (completing Suski's observations with fecal matter), that a variety of colon bacillus, or its toxin, found in drinking water, was the main cause of goiter, affords the foundation for its rational treatment. Briefly, the aim should be to **eliminate the cause,** external or internal, whatever that may be, and *if this is done early enough,* the case will never reach the surgeon.

General Measures.—The first step then is to carefully examine the tonsils, the nasopharyngeal tract and the sinuses, the teeth, and also the intestinal canal and the pelvic organs, etc., for any chronic, especially suppurative disorder which may be present. The author has seen goiters disappear automatically and without internal treatment after **diseased tonsils** were **removed.** Any condition capable of causing a toxemia which in turn provokes a defensive reaction on the part of the thyroid should be eliminated.

In the intestinal canal ptosis of the transverse colon, or prolonged cecal retention of feces, are frequent causes in sporadic cases. **Intestinal lavage** with warm saline solution, with the buttocks elevated and the patient lying on the right side, or saline **aperients,** preferably **sodium phosphate,** 2 drams (7.8 grams) in a glassful of hot water, taken night and morning, are efficient measures to correct this cause. **Intestinal antiseptics** and **purgatives** are often efficient in appropriate cases, even where intestinal atony and other commonplace causes of constipation prevail. Messerle[34] tried **benzonaphthol** in 2 cases in the dose of 7½ grains (0.492 gram) three times a day, in cachets; **thymol** in 2 cases, 1½ grains (0.097 gram), with milk sugar in cachets, twice daily; **phenyl salicylate,** in 3 cases in the dose of 15 grains (0.972 gram) in tablets, twice daily; **creosote** in 2 cases in doses of ¾ grain (0.048 gram) in pills, three times a day; in 2 cases laxative tablets, each containing ¾ grain (0.048 gram) of **aloes,** 1½ grain (0.097 gram) of **resin of jalap,** and 7½ grains (0.492 gram) of **rhubarb,** every evening. The results were similar, whatever drug was used, and consisted in the diminution of the neck circumference by from 2.5 to 5.5 cm. within a period of from twenty-one to thirty-eight days, with the exception of one case in which the laxative combination was used, and in which a diminution of only 1.5 cm. was noted.

The results confirm those of McCarrison, who after inducing goiters by the ingestion of polluted water, caused them to disappear by administering intestinal antiseptics, such as thymol, or anti-colon-bacillus and anti-staphylococcus vaccines. They are likewise in accordance with the observations of Gaylord and Plehn, who brought about slow regression of goiters in fishes by adding minute amounts of **mercury bichlorid** and **potassium iodid** to the water of the ponds in which they were kept. The laxative tablets were, of course, not expected to exert an antiseptic influence, but were intended to act mechanically, diminishing the number of bacteria in the bowel. All these results indicate that intestinal stasis, however caused, entailing the prolonged retention of fecal microorganisms or their toxins, may provoke a toxemia capable, in turn, of causing goiter.

CURATIVE TREATMENT.—In some instances, such as cases of goiter in adolescents, young girls, etc., or those due to heredity, or focal lesions in the gland during acute febrile diseases, the swelling is merely due to an effort on the part of the gland to compensate through increased activity for its deficient power. More arterial blood is admitted to the organ, its secretory activity is greatly increased, and it becomes enlarged when the process is prolonged. **Iodin** in organic combination being the active principle of the thyroid secretion, the use of this halogen is indicated. If the goiter is absolutely non-toxic and causes no increase in the pulse-rate, **thyroid gland** in very small doses, for instance ½ grain (0.032 gram) three times a day, with **iron** if there is anemia, will often cause the goitrous swelling to recede. Attention must be paid to the bowels. Sometimes the **iodids,** especially the sodium iodid in 5 grain (0.324 gram) doses, in a tumblerful of water after meals, or drop doses of soluble iodin, will be better borne. The latter is also used as a prophylactic.

It should be borne in mind, however, that cases of chronic goiter of the endemic type, particularly if the latter is dense or hard under palpation, often do not bear any preparation of iodin well. It is not taken up by the gland, and acts as a general toxic. In one of the writer's cases, one drop daily of liquid iodin sufficed to cause severe cardiac distress. Again, any iodin preparation is contra-indicated when there are pressure symptoms. All cases treated with iodin preparations should be closely watched lest symptoms of hyperthyroidism or of iodism occur.

In patients who bear iodin preparations well, the disappearance of the growth is promoted by applying a 5 per cent. ointment of **iodopetrogen** (N. F.) over the goiter before retiring, and washing it off in the morning. A piece the size of a small hazelnut is rubbed in daily until the skin begins to be irritated. Sometimes a weaker ointment is required, particularly when the skin is unusually sensitive. A preliminary gentle massage of the goiter tends to promote constriction of the dilated blood-vessels reflexly. E. Myers[35] recommends the introduction of **potassium iodid** by means of cataphoresis.

It should always be borne in mind in these cases that the distance between insufficiency of a given gland and the threshold of efficiency may be very slight, and that the gland may become fully active before recession of the goiter has occurred. In such cases, toxic symptoms with tachycardia may appear. Hence the reiterated admonition to watch such cases closely. A few days' cessation of the remedy may then be ordered, after which a smaller dose is resumed. If toxic symptoms persist, however, **Fowler's solution,** 2 minims (0.12 c.c.) twice daily, in half a glassful of water, will soon overcome them.

Vaccines prepared from coliform bacilli derived from the patient's stools have been tried, resulting in a more or less temporary diminution in the size of the goiter. Unless, however, the source of general toxemia, *i.e.*, the intestinal contents, is kept within non-toxic bounds by purgation, intestinal antisepsis, etc., vaccines prove useless. They are therefore unnecessary, since purgation, etc., produces even better results.

The use of **x-rays** has been advocated, but recent investigations have shown that while the activity of the gland is increased, the patients often show more or less severe general symptoms with enlargement of the goiter due to an initial stimulating effect on the gland. As symptoms of hyperthyroidism have been known to persist, the treatment is not to be recommended in view of the more rational methods now available, based upon elimination of the cause. Again, should large doses be employed and surgical measures become necessary, the adhesions which, according to Eiselsberg, follow *x*-ray exposures, might render the operative procedure more difficult. Additional experience may, however, eliminate what drawbacks roentgenotherapy seems to present.

Although Tansini[36] has in recent years revived the obsolete method of injecting iodin into the gland, emphasizing that it is indicated only in cases of parenchymatous goiter, the fact remains that it has caused numerous deaths and that such risks are not warranted, at least in non-toxic goiters which can be cured by less dangerous methods. The use of injections of **hot water, quinin, urea** and other agents will be reviewed under Hyperthyroidism.

Surgical measures are said to be indicated when all other methods have been tried and have failed. It becomes a question, however, whether the medical measures or ''methods'' utilized have not been perfunctory and purely empirical. A cursory view of the average textbook will show that elimination of the cause in sporadic cases is not even referred to, except perhaps a change of water, which seldom plays a rôle in such cases in other than endemic districts. When these few words: *early elimination of the cause* have become the slogan of goiter therapy, there will be no further use for surgery in such cases. What this means may be indicated by the fact that a recent report from the Mayo Clinic referred to 5,000 ''non-symptomatic, *i. e.*, non-toxic'' cases operated in that clinic.

If the patient has received the benefit of modern medical treatment, *i. e.*, treatment such as that described above, in which empiricism plays no rôle, and the results are not satisfactory, it is because the structural changes in the gland are such as to preclude any extensive reduction by measures other than removal.

Ligation of some of the **arteries** supplying the growing gland has been extensively resorted to, but experience has shown that even where four or more arteries are ligated recurrence of the goiter is not prevented. A study of the cases reported by Roux (probably the first surgeon after the late Professor Kocher in Switzerland), and by Sarkissiantz,[37] illustrates this fact, and shows that ligatures promote a very abundant formation of connective and vascular tissue, leading in turn to the formation of conglomerate cysts, which not only tend to cause dangerous pressure nodules, but render any future operation very difficult. A simple, unilateral, well-performed operation is preferable.

In Switzerland the operative mortality has been reduced, since 1870, from 12.5 to 0.066 per cent.; under the régime of such a surgeon as the late Professor Kocher it has fallen to 0.003 per cent. This indicates the importance of entrusting patients only to highly trained men. In the practice of such men, the operative mortality is now practically *nil.* A feature of importance in this connection, moreover, is that a well-trained surgeon will not remove sufficient thyroid tissue (not to speak of the parathyroids, which even a tyro would not remove nowadays) to induce in the patient a state of postoperative asthenia or larval myxedema. These conditions will be described later in this article.

Kocher, in one of the closing addresses (1917) of his vast experience, urged that removal be limited to that part of the gland which exerts pressure, that as much as possible of the functioning gland should be left, that ligature of the arteries should be avoided as much as possible, and that the whole gland should never be removed. He stated that the main point to be borne in mind is to leave sufficient functionally capable tissue to avoid subsequent hypofunction.

At the present time (1919) the general consensus of opinion among surgeons is that surgical treatment is demanded: (1) when the goiter is large, to correct disfigurement, (2) when pressure is exerted on the trachea, esophagus, larynx or other cervical or thyroid structures, (3) when enlargement of the goiter is rapid, or a malignant process is suspected, (4) when symptoms of hyperthyroidism, especially of tachycardia, appear.

When the general practitioner learns to attach due importance to any, even the slightest enlargement of the thyroid gland, and to begin his treatment by removing the cause at the earliest possible moment, even the partial sacrifice of this useful organ by surgical means will become a thing of the past.

In congenital goiter and goiter in the newborn due to obstetric pressure, the various forms of **artificial respiration,** together with the use of **oxygen,** are helpful. If dyspnea persists, **section of the isthmus,** or **exothyropexy,** will give immediate relief. **Tracheotomy** is **contra-indicated,** although **intubation** has been employed. Thyroid substance or sodium iodid given to the mother may at times lead to the disappearance of the goiter in both mother and child. In the congestive form of the disorder, **cold compresses** should be applied to the neck and **warm foot baths** or hot baths given.

Pathology.—Until recently it was believed that the benign or non-toxic parenchymatous goiter was attended by hyperplasia of the organ, but the recent histological examination of 5,000 specimens of benign goiters after their removal at the Mayo Clinic led L. B. Wilson[38] to conclude that both hypertrophy and hyperplasia of the parenchyma were absent. He occasionally observed small islets of tissue composed of large cells which appeared to be actively functioning, but these islets were sufficiently minute to suggest that they might not suffice to awaken general symptoms. Others have observed enlargement of the glandular elements, the follicles being increased in number and containing a correspondingly greater quantity of colloid. Such goiters are in the category with those referred to as occurring during adolescence, during pregnancy, and, though relatively rarely, during lactation and menopause. They occur also as a result of acute infections, but here—a feature too often overlooked by pathologists—they often cause the formation of hemorrhagic foci. These, being followed by the formation of as many sclerotic areas, may greatly hinder the mental and physical development of the child. Of the children's diseases, diphtheria and scarlet fever are most to be feared in this connection. Another feature which is rarely mentioned, notwithstanding its importance, is the marked hyperemia, a point to be borne in mind when medical treatment is initiated.

While the histological characteristics just described may be said to apply to the many sporadic cases met with in practice, the histological changes observed in endemic cases, those met with in goiter districts, are of the colloid type. Wilson,[39] referring to these goiters, states that "there is little doubt that a water-borne low-grade infection is a large, if not the only, factor in the development of this most common kind of thyroid enlargement"—the fecal or *Bacillus coli* type of Shiga, McCarrison, etc. About 9 per cent. of the goiters studied by Wilson were diffuse colloids showing some tendency to regeneration of the atrophic parenchyma by the formation of new follicles in the walls of the old distended follicles; about 26 per cent. were largely or wholly encapsulated adenomata, while about 64 per cent. were large glands with a few small adenomata, or none at all; in these glands the follicles were distended with dense colloid, the parenchymal cells being flattened and functionless.

It has generally been thought that the colloid represented the secretion of the gland owing to the presence in it of iodin, but the researches of Kendall have tended to show that the secretion is a product of the cellular elements *per se*. Under these conditions it appears to the writer of the present article that the colloid serves to store the iodin pending its utilization by the cellular elements in the elaboration of the glandular secretory product.

Geographical Distribution.—Although goiter may, and often does, occur as a congenital disease, the vast majority of cases encountered in practice are endemic, large numbers being found in groups in particular districts or regions. Switzerland is studded with endemic foci. This applies also to various mountainous districts of southern France, particularly the Alps and Pyrenees. In some regions of Spain, the province of Avila, for instance, the disease is exceedingly common. According to Goyanes,[40] in one district with 1,780 inhabitants every one of the young men registered for military service in the year 1914 had to be rejected on account of goiter. The Carpathians, the site of formidable battles between the Austrians and Russians during the recent war, and also Germany, contain many foci. In some towns of Bavaria, according to Lobenhoffer,[41] from 21 to 26 per cent. of the inhabitants have goiter. Norway and other Scandinavian countries, and the Netherlands, particularly Utrecht and Amsterdam, also contain goiter districts. An examination of nurses and attendants in the public hospital of Utrecht showed that 11 per cent. had goiters; the proportion elsewhere in Holland reached 16 per cent. The prevalence of goiter among Dutch recruits is also large, according to Kappenburg.[42] The disease is also common in England, notably along the valley of the Thames.

The United States also contain many goiter districts. It was formerly thought that the states in the Great Lakes region were among those with the highest percentage of the various forms of goiter, but an examination of over 65,000 men at Jefferson Barracks by Lieut. F. M. Smith[43] showed that such was not the case. As can be seen from the following chart (Table 1) Oklahoma, Texas and Tennessee are greatly in the lead:

TABLE I

INCIDENCE OF GOITER IN RECRUITS FROM THE MIDDLE WEST STATES
(*F. M. Smith*)

States	Number of Men Examined	Number of Goiters	Percentage of the Number Examined	Number of Toxic Goiters	Percentage of Goiters with Toxic Symptoms
Arkansas	4,375	104	2.3	11	10.5
Illinois	24,836	158	0.63	16	10.1
Iowa	998	62	6.2	7	11.2
Indiana	1,465	97	6.6	7	7.2
Kansas	1,792	21	1.1	3	14.2
Michigan	211	7	3.3	0	0
Minnesota	7,551	78	1.3	3	3.8
Missouri	19.577	221	1.1	28	12.6
Nebraska	124	10	8.0	1	10.0
North Dakota ...	523	46	8.7	9	19.0
Oklahoma	221	84	38.0	7	8.3
South Dakota ...	387	24	6.2	1	4.1
Tennessee	485	56	11.0	7	12.5
Texas	141	29	20.0	6	20.0
Wisconsin	2,821	77	2.7	10	13.0
Grand Total ..	65,507	1,074	1.63	116	10.8

Although these figures may not portray the true situation with precision, since all the men from Texas, for instance, may have come from a goiter district, while those from Michigan may have lived in goiter-free regions, the fact remains that they indicate the widespread distribution of the disease in the Middle West, which only exemplifies a state of things existing in many other states, in the East, South and West. Maine, for example, has several foci, likewise Georgia and other southeastern states, Oregon, Montana and Utah. In the North Ogden district, for instance, at the foot of the mountains north of Ogden, the population of which is only 1,090, according to Pidcock[44] practically ¼ of the females have goiter; nearly all of these individuals have lived in the district all their lives. The disease is also encountered in Canada, particularly in and around the Laurentian mountains, where it is known as "grosse gorge." South America, particularly Bolivia, also contains foci, which are likewise common in the Philippines, India and China. On the whole, goiter and its kindred disorder, cretinism, may be said to occur in all countries, regardless of race.

ACCESSORY NON-TOXIC GOITERS

While, as stated, the word "goiter" usually applies to enlargement of the thyroid gland proper, thyroid tissue often occurs elsewhere and becomes the seat of goitrous and other forms of growth.

Accessory thyroids, which are vestiges of proliferated tissues of the thyroglossus duct, may be found anywhere below the main gland down to the arch of the aorta, the bifurcation of the trachea, between the latter and the esophagus, the mediastinum, and the ovaries. More commonly, however, they are found about the hyoid bone and at the base of the tongue. They all show the histological structure of thyroid gland, including the colloid follicles.

Accessory glands sometimes constitute the only thyroid tissue which carries on thyroid functions in the subject. Surgical removal of such tissue would, therefore, be followed by myxedema. Hence it is of the greatest importance in all such cases to ascertain whether or not the thyroid gland proper is present before operating at all, or at least, as in lingual goiter, to énucleate only a portion of the growth.

Lingual goiter is the form most frequently observed among those developed in the accessory glands. It occurs oftener in women than in men, and at all ages, although the majority of cases reported occur about puberty. In true lingual goiter the growth is situated upon the back and dorsum of the tongue behind and below the foramen cecum in the median line. It is more or less imbedded in the tongue, forming the *intralingual* goiter, or it forms mainly under it, being manifest under the chin, and constituting the *sublingual* goiter. For diagnostic purposes it is well to remember that in either of these situations thyroid tissue is liable to the same pathological conditions which affect the thyroid gland, including, besides the various types of goiter, the various malignant growths, such as sarcoma of rapid growth, and carcinoma, all of which seem to be unusually painful in this situation. Lingual thyroid tumors may also be benign, or become the seat of gummata, calcareous deposits, dermoid cysts, etc.

Symptomatology.—The symptoms of lingual goiter, wherever situated, are characteristic in the sense that they soon cause considerable discomfort. This is mainly due to the fact that, owing to their very great vascularity, which extends to the tongue itself, marked tension and fullness are experienced, the mass conveying the sensation of a large foreign body. Speech soon becomes impeded, and also deglutition. Dyspnea may occur later, the time of onset varying with the location of the growth; thus, the dorsal or true lingual goiter tends to produce it in two ways: (1) by pressing down the epiglottis posteriorly, and (2) by tending to block the pharyngeal area through its own weight when, particularly during sleep, the lingual musculature is relaxed and the patient lies on his back. Cough is another common symptom due to pressure upon the back of the epiglottis. The surface of the growth being fragile and often ulcerated in advanced cases, it bleeds readily when touched with instruments; the saliva may be streaked with blood.

While palpation, internal, external and also bimanual, aids inspection in revealing the presence of a lingual growth, which in sublingual goiter may be accompanied by a localized swelling under the chin, the laryngoscope will alone afford a clear idea of the identity of the neoplasm, a bosselated swelling about the foramen cecum showing enlarged bluish vessels, which are painless on pressure.

Treatment.—The treatment is **surgical**, but it sometimes happens, as previously stated, that the affected gland is the only thyroid body which the subject possesses; removal under these conditions, therefore, would entail myxedema. If operative procedures cannot be resorted to, the various measures used in the treatment of true goiter may be employed also. **Astringents, silver**, particularly **nitrate**, may be used in a strong solution, 60 grains (3.90 grams) to the ounce, to contract the blood-vessels. This must be applied carefully with a pledget of cotton on a curved stylet, and dripping or oozing of the solution from the cotton into the neighboring cavities should be avoided. But as a rule these methods prove **useless**. **Hot water** or **quinin** and **urea injections, punctures** or **galvanocautery** are **dangerous** in this situation, owing to the probability of causing edema of the laryngeal tissues, and asphyxia. Partial **enucleation**, with the tongue drawn out, is the most successful and safe procedure, care being exerted to control hemorrhage.

MALIGNANT GOITER

Malignant goiter, observed in less than 1 per cent. of cases subjected to operation, usually occurs as a complication of goiters of long standing. Carcinoma is the type usually observed, but sarcoma and malignant adenoma are occasionally encountered.

Symptomatology.—Pain in a pre-existing goiter, which cannot be attributed to inflammation or strumitis, suggests malignancy, especially in the presence of a cachectic facies. The surrounding lymph-glands are usually involved early and metastases are often observed in the bones, but the surrounding structures may be invaded. Radiating pain, hemoptysis or hemorrhage from vessels in these areas, or tracheopharyngeal fistula, pus and detritus in the sputum, are suggestive signs. Carcinoma of the thyroid is usually nodular, while sarcoma is generally smooth.

Occasionally, accessory thyroid glands, situated between the trachea and esophagus or behind the latter, develop malignancy.

Treatment.—Early **operation** is indicated, the whole gland being removed but its capsule preserved whenever possible. In late malignancy with lymphatic involvement, operation is hardly to be recommended, except for the relief of pressure symptoms, as it may accelerate the growth of the tumor. By far the most satisfactory method, however, is the use of *x*-rays when the case is not too far advanced.

THYROIDITIS (INFLAMMATION OF THE THYROID) AND STRUMITIS (INFLAMMATION OF A GOITER)

Inflammation of the thyroid may be caused by the pathogenic organisms of various diseases: typhoid, influenza, pneumonia, rheumatic fever, erysipelas, tuberculosis, adenitis, dysentery, syphilis, tonsillitis, pyemia, scarlet fever, diphtheria, parotitis, etc.; or by various agents such as lead, iodin, and toxins; or again, by parasites, such as echinococcus, the organism of actinomycosis; the malarial hematozoön, the *Schizotrypanum cruzi* of Chagas, etc.; and finally by traumatism.

The condition may be acute or chronic, and in most instances observed it is due to secondary invasion of the glands by germs in the course of systemic or localized disorders.

Thyroiditis may complicate a goiter and be caused by the same etiological factors, but it has also been brought on by therapeutic injections of iodin and other agents or by traumatism of the goitrous mass. Thyroiditis of a goiter is known as strumitis. In both thyroiditis and strumitis, the infection may be due to the extension of an infection from a neighboring focus, to infection by a septic instrument, whether it is an incision or a puncture, or, finally, it may come through the blood, the volume of which received by the gland is relatively enormous.

A peculiarity of the gland, however, is that it is often able on its own account to destroy pathogenic germs, owing to the sensitizing action it has upon them, as previously shown. In other words, its hormone renders vulnerable to the proteolytic activity of the antibodies all organisms present in the tissues invaded, and it is only when the invasion is unusually great or the gland itself is pathological, as it is in true goiter, that the stage of abscess is reached.

Symptomatology.—It is important to bear in mind in this connection that the thyroid may become greatly enlarged in the course of an infectious disease and yet show no sign of inflammation postmortem. This may also occur during pregnancy, and the gland may recede physiologically after parturition, thus ceasing its exacerbation of defensive activity. In the presence of a thyroid swelling, therefore, inflammation may not be present. Indeed, this morbid process, particularly when attended by suppuration, is comparatively rare when no open lesion of the organ is to be found.

When hyperemia alone is present, slight swelling of the gland, with some tenderness and dysphagia, are noticed. In acute thyroiditis, however, severe local as well as general manifestations occur, a chill marking the usually sudden onset, which is followed by considerable swelling of the gland, marked dysphagia and radiating pains, intense dyspnea from tracheal compression, and possibly paralysis of the recurrent laryngeal nerve or edema of the glottis. Fever may be high, in spite of the absence of suppuration, and the tachycardia typical of thyroid overactivity has also been observed to occur independently of fever. In a few days, as a rule, the morbid condition subsides; resolution without suppuration occurs in 40 per cent. of the cases. Where suppuration does develop, the abscesses are as a rule multiple, each, however, tending to break through the adjoining soft tissues, thus leading to confluence, and to rupture through the skin or purulent infiltration of surrounding structures. At times this may lead to dangerous complications such as pneumonia and pyemia. The abscesses bleed easily and severe capillary hemorrhages sometimes constitute a complication. The toxic form due to lead, to the iodids in excessive doses, or given in the presence of a thyroidal inflammatory process, etc., gives rise to similar symptoms.

The wealth of the thyroid tissue in vascular channels is such that, even in the absence of actual thyroiditis, a high blood-pressure, such as that of fevers, may lead to interstitial hemorrhages. Either through subsequent interstitial sclerosis or because of degeneration of the epithelium in thyroiditis, the thyroid functions may become so impaired as to lead to marked evidences of hypothyroidism or even typical cretinism. On the other hand, as pointed out by Theisen,[45] hyperthyroidism may develop, after thyroiditis complicating acute tonsillitis.

Chronic thyroiditis may follow the acute type, resolution having been incomplete. Oftener, however, it accompanies such chronic disturbances as syphilis, tuberculosis, actinomycosis, and echinococcus disease. The resulting ultimate reduction in thyroid activity is a most common cause of hypothyroidism, and, in children, may thus lead to deficient physical and mental development, and even to idiocy.

Treatment.—The thyroid should be carefully watched in *all* infectious diseases, and where local pain, tenderness, or swelling develop, **cold compresses** should be applied, not only in order to cause contraction of the vessels beneath but also to reduce the local temperature and thereby also the activity of the protective principles concentrated in the thyroid which, in thyroiditis, probably exceed the limits of beneficial action and lead to autolysis of the gland-tissue. **Saline solution,** by mouth, rectum, or the subcutaneous route, is also of importance in these cases. A high blood-pressure, tending to perpetuate thyroid congestion, may at times be advantageously lowered through the use of such agents as **chloral hydrate** and **Veratrum viride.** As in other local inflammations, **rest** is an important measure, and **leeching** may exert a useful decongestive effect. For dyspnea of alarming degree **tracheotomy** may be required.

Inasmuch as suppuration occurs in approximately half of all cases, the frequent advisability of **surgical intervention** must be borne in mind. The presence of pus being difficult of demonstration, exploratory puncture may prove of assistance. According to Kocher,[46] if incision does not result in rapid recovery, multiple abscesses should be suspected. Persistence of a sinus points to extensive necrosis; the affected half of the gland should then be excised.

In chronic thyroiditis leading to hypothyroidia, **thyroid treatment** should be instituted. Removal of chronically diseased thyroid tissue may be advisable, particularly where dyspnea is troublesome. DeMassary[47] has reported a case of chronic syphilitic thyroiditis with marked impairment of the intellectual powers in which thyroid medication restored the mental condition, and **mercury**, begun only six months later, reduced the thyroid gland, previously large and soft, to more nearly normal dimensions.

HYPERTHYROIDIA OR HYPERTHYROIDISM (GRAVES' DISEASE, BASEDOW'S DISEASE OR EXOPHTHALMIC GOITER)

Definition.—This disease is due to toxemia of focal, systemic or neurogenic origin, which, by provoking a defensive reaction of the thyroid apparatus, causes it to secrete its physiological hormone in excess, thus provoking in all tissues, including the nervous system, correspondingly active and destructive catabolism.

Etiology and Pathogenesis.—It is no longer necessary, in the light of present knowledge, to defend the view that Graves' disease is due to excessive activity of the thyroid gland. So solidly based is this fact on both experimental and clinical data that the term "hyperthyroidism," or its more correct synonym "hyperthyroidia," is being increasingly adopted by men whose experience is greatest in the study and treatment of the disease. Its adoption is all the more warranted in that, as we shall see, it does not entail elimination of the "nervous theory," long deemed by many to be the predominating one, since it is well known to-day that the sympathetic system is markedly involved in the morbid process. Nor can the "thyrogenital theory," the "thyro-hypophyseal theory," the "thyrothymic theory," the "thyropancreato-adrenal theory," nor even the "neurothyro-adrenal theory" be set aside, since each one of the organs named in the various designations can be shown to participate more or less actively or passively in the pathology of the disease. Even W. H. Thomson's theory that the disease is due to auto-intoxication of intestinal origin, with the thyroid taking but little if any part in the process, has contributed its share to our knowledge. We know to-day that enlargement of the gland is not a necessary accompaniment of its excessive secretory activity, and that the latter, *i.e.*, hyperthyroidia, may be caused not only by intestinal auto-intoxication but also by a multitude of poisons, both inorganic and organic, including bacterial toxins, fatigue wastes, etc.

Toxemia Genesis.—This feature of the pathogenesis of hyperthyroidia was well summarized by Major McCarrison.[48] He wrote in 1913, referring to the writer's conclusion in 1903, that the injection of various toxins into man and the lower animals excited, more or less actively, according to their virulence, the thyroid gland's functional activity: "The fact that the antitoxic and bactericidal resources of the body are largely dependent on the functional perfection of the thyroparathyroid mechanism is, I believe, as clearly established as is the influence of this mechanism on metabolism. . . . Farrant, also, has lately induced marked thyroid hyperplasia by the injection of diphtheria toxin into guinea pigs; he demonstrated that the hyperplasia so induced could be controlled and greatly mitigated by the administration of thyroid extract at the same time as the toxin. Fassin found that the germicidal power of the blood was diminished by thyroidectomy. Charrin, Vincent, and Jolly drew attention to the fact that animals deprived of their thyroid glands are rendered very susceptible to infectious diseases, to which they readily succumb. Hürthle observed that by ligaturing the bile-ducts in dogs the thyroid secretion was increased; he attributed this change to the passage of certain constituents of the bile into the blood. Turro has found that the juice of swine's and sheep's thyroids almost entirely dissolved the comma, typhoid, and anthrax bacilli, as well as *Bacillus coli communis* and streptococcus. Gley showed that the blood-serum of thyroidectomized dogs is more toxic than normal serum, and gives rise to convulsions when injected into animals, while de Luca and d'Angerio have found that the urine of these animals contains a higher percentage of toxic substances than is normal, and that thyroid extract administered to them counteracts this toxicity."

To these data many may be added. Thus, we have seen that endemic goiter was caused by water-borne toxins derived from *pathogenic organisms,* in all likelihood a variety of colon bacillus, as shown by the researches of Susuki and McCarrison. De Quervain found that the injection of bacterial toxins caused a marked hyperplasia of the thyroid gland corresponding to that produced by Bircher in rats by the administration of water from goitrous wells. Halsted also found, in 1913, that the portion left after partial removal of the thyroid could again become hyperplastic if infection of the wound was not prevented by strict asepsis. Practically all the *febrile infections* have been known to cause hyperthyroidism or Graves' disease: typhoid fever, scarlet fever, acute articular rheumatism, influenza, meningitis, peritonitis, variola, hydrophobia, puerperal infections, measles, etc., with typical histological lesions in the thyroid denoting excessive functional activity and proliferation of glandular tissue removed either during life or postmortem. All this applies also to various *poisons,* notably phosphorus, turpentine, silver nitrate and pilocarpin, also to the wastes, toxins and detritus added to the maternal blood during pregnancy by the fetal organisms, which participate in the genesis of puerperal septicemia.

Any of the foregoing disorders which assume chronicity tend, particularly in predisposed individuals, to bring about and sustain the thyroidal morbid process. Chronic *infections* of the *nose, nasal sinuses, nasopharyngeal space,* and, particularly, of the *tonsils*—after, perhaps repeated attacks of tonsillitis—are often encountered. The tonsillar infections, carious teeth and pyorrhea alveolaris in particular, greatly predominate in the causation of the Graves' syndrome. In fact, the condition often disappears soon after the causative infection has been removed. This applies likewise to coprostasis; when adequate measures are resorted to to eliminate the fecal masses the retention of which promotes and sustains the pathogenic toxemia, the latter disappears. On the whole, as Crotti[49] states: "the protean origin of Graves' disease is no more a puzzle; the remote causes of it are indeed numerous and diverse; as: infectious diseases, disturbed polyglandular function, chemical agents, etc., but the immediate cause is always the same, *the hyperfunction of the thyroid.*"

Why is it always the same and what is the nature of the function which all the toxic factors enumerated and many others not mentioned actively exaggerate?

The answer to this question is embodied in Beebe's[60] succinct, although clear summary of the writer's view, *viz.:* "Sajous has advanced the hypothesis that the mechanism of the defense against infections depends to a large degree on thyroid function." We have seen, at the beginning of the preceding section, that this function was attributed by the writer, many years ago, to the thyroparathyroid mechanism, in addition to and as a part of the function generally accorded it, *i. e.,* of influencing metabolism. This hypothesis has been confirmed both experimentally and clinically, and, furthermore, it affords the keystone upon which rests the rational treatment of the disease. The defensive effects noted have been attributed to "a marked alteration in the metabolic processes of the animal rather than to a mechanism of protection." But the fact that the latter is so closely interwoven with that of metabolism that they cannot be separated indicates the invalidity of any such objection. In other words, the well-known acceleration of metabolic rate brought about by the administration of thyroid gland is at the same time the process through which the protective power is exercised; precisely as thyroid is known to break down, *i.e.,* catabolize, fats, so it also breaks down, and catabolizes many varieties of bacteria, their toxins and other poisonous substances.

Again, Reid Hunt having found that thyroid feeding protected white mice from acetonitril poisoning, while rats and guinea pigs were rendered more susceptible to this poison by thyroid, it has been contended that the protection afforded by the thyroid gland can not be a universal phenomenon. This objection serves only to establish the protective function on a solid footing. In the first place, the writer of the present article has never claimed that the function referred to was a universal phenomenon in that it protected the body against all forms of intoxication. What he does claim, on the basis of close observation, is that only bacterial toxins or other poisons, organic or inorganic, which are capable of acting as antigens are also capable of provoking hyperfunction of the thyroid. Many agents: arsenic, the cyanids (acetonitril, used by Reid Hunt, is converted in the tissues into a cyanid), the bromids, the salicylates, ergot, the coal-tars, etc., are known in fact to depress the functions of the thyroid gland, just as they are known to inhibit the systemic defensive resources. It is through them, indeed, that *excessive activity* of the organ, *i. e.,* hyperthyroidism, or Grave's disease, is actively controlled.

PSYCHONEURAL GENESIS.—Fright, particularly if accompanied by traumatism, is a prominent cause of hyperactivity of the thyroid gland. This was very marked in one of the author's cases, which was due to the fall of an elevator eight stories. Fright was clearly the only cause, an air cushion provided as double security having caused the elevator gradually to lose all momentum before it reached the ground, thus avoiding all traumatism to its occupants. The patient, a man of thirty-two years, who was previously in excellent health, volunteered the information that he had been "greatly frightened." The typical symptoms of hyperthyroidism appeared in a week during which he was "extremely nervous." In another case known to the author, which was due to the collision of a street-car with the patient's limousine, both fright and traumatism played a pathogenic rôle. A second similar collision, although without traumatism, in the case of this patient, a young woman of twenty-six years, caused a recurrence of the severe condition which the first accident had caused, and from which she had practically recovered. As recalled by Beebe,[51] cases of severe hyperthyroidism were numerous after the Kishinev massacre in Russia and the San Francisco earthquake. The exigencies of service in the field, the intense excitement, stress and apprehension provoked by modern methods of warfare, shell-fire, bombs, rapid-fire guns, etc., in the Great War, provoked marked Graves' symptoms in many men who had previously had small goiters. Bénard[52] observed symptoms in previously well men also, after sudden violent emotion, great anxiety and strenuous exertion. Léniez[53] observed typical Graves' disease in the case of 3 military men soon after they had fallen from their horses, striking their heads on the ground.

Fright—plus *traumatism* in many instances—has long been recognized as a cause of Graves' disease, forming, in fact, one of the strongholds of the "nervous theory." Indeed, the symptoms of both conditions are at least very similar. Darwin and Sir Charles Bell, according to Carter,[54] described a person in intense terror as follows: "The heart beats quickly and violently, so that it palpitates or knocks against the ribs; there is trembling of all the muscles of the body; the eyes start forward and the uncovered and protruding eyeballs are fixed on the subject of terror; the skin breaks into a cold and clammy sweat, and the face and neck are flushed or pallid; the intestines are affected."

What is the underlying cause of this similarity? How can so remote a factor as fright, to which might be added deep grief—a frequent cause —anger, and many other conditions in which the emotions are violently stirred, awaken precisely the same morbid process in the thyroid gland as do a multitude of poisons, and thus cause excessive functional activity of that gland? Again we find, on analysis, a toxin as the pathogenic factor.

Chromatolysis, often mentioned by Crile, denotes more or less disintegration of a certain component of the nerve-cells—their chromatin. As far back as 1903 the writer of the present article was convinced that nerve-cells received blood-plasma containing adrenal substance, which was converted in turn into oxyhemoglobin (adrenoxidase). He also traced the latter in the axis-cylinders (into which, as is well known, the toxin of tetanus—tetanotoxin—also gravitates), in the cell-body, the neurofibrils, etc., of the neuron or nerve-cell. Every link of this chain of events has since been corroborated by the observations of others. Lichwitz has shown that adrenalin gravitated to the nerves; Macallum, of Toronto, found that sympathetic nerves contained a substance resembling adrenalin, and Menten, of Chicago, found that the adrenal product did become converted into oxyhemoglobin. On the whole, the writer considered that the nerve-cell lived and breathed, so to speak, as do other body-cells, but that the adrenals and thyroid hormones took part in the process.

As regards the influence of excessive mental stress, fear, anger, etc., upon this process, Vas, Mann, Lambert, Lugaro and others showed long ago that nerves fatigued by stimulation lost this substance more or less rapidly. This fact is quite in keeping with Crile's more recent clinical views, and with those of Cannon. Briefly, fright, anger, etc., bring about the disintegration of the nerve-cell, by subjecting it to violent stimulation, which means excessive metabolic activity. And it is here that the primary toxin or cause of exophthalmic goiter in these cases appears, *e.g.*, excessive metabolism of the nerve-cell is known to produce phosphoric acid, cholin, and also, especially, a substance known to be particularly poisonous, *neurin*, a body closely allied to muscarin. So sensitive is the thyroid gland to the latter poison, in fact, that it was once believed that the one function of the organ was to destroy neurin as fast as it was formed. In the light of these facts, therefore, we again realize that a poison, although neurogenic in this case, may become the primary cause of the disease.

But why, once the excessive stress due to fear, rage, etc., is terminated and entirely appeased, does the morbid process continue? Why do all the morbid symptoms, particularly those of nervous origin, persist? This is due to a vicious circle. The thyroid, powerfully stimulated to react against the intoxication, itself becomes a destroyer of the nerve-cell. This becomes intelligible when we recall that, besides containing chromatin, the nerve-cell is likewise rich in fatty substances, lecithin (containing stearic, palmitic or oleic acid) in particular. If we also recall the familiar fact that thyroid gland first attacks fats, breaking them down sooner than it does any other tissue, we realize why it is that excessive thyroid activity so actively disturbs the nervous system. Briefly, a severe mental stress, fear, rage, deep grief, etc., causes excessive catabolism in the nerve-cells, and the excretion by them of highly toxic wastes, including neurin; these poisons, by provoking a defensive reaction of the thyroid, cause it to break down fats, including the fatty components of the nerve-cells, thus establishing a vicious circle by perpetuating the catabolism of these and the formation of poisons.

This accounts for the severity of such cases, unless, as we shall see, they are treated, not symptomatically, as is now generally the case, but in such a way as to arrest the excessive thyroid activity. It accounts, moreover, for the well-founded contention by many authorities that exophthalmic goiter is a nervous disease.

We thus find that hyperthyroidism or Graves' disease is due primarily to some toxin originating from a pathological process in one or more organs, either the tonsils, sinuses, nose, nasopharynx, teeth or gums, stomach, intestines, genito-urinary organs, etc., or to some toxin formed in the cerebrospinal neurons subjected to stress: cholin, phosphoric acid and, particularly, neurin, a highly poisonous waste-product.

Another source of toxemia, however, consists in the fact that any one of these poisons further excites the thyroid apparatus to supranormal activity, owing to the active part taken by this apparatus in the defensive functions. The thyroid hormone being thus produced in excess, it breaks down not only fats throughout the body at large, but also the *fatty bodies in the nerve- and brain-cells.* In all cases, therefore, whatever their origin, destructive nerve-tissue catabolism occurs. This accounts for the nervous phenomena which play so prominent a part in the symptomatology of the disease, while the excessive catabolism induced explains the emaciation, which sometimes progresses extremely rapidly, observed in severe cases.

To the neurogenic wastes thus produced in all cases must be added the waste products of all other tissues subjected to excessive catabolic activity by the overactive thyroid apparatus; these wastes goad the latter to still greater activity.

Hyperthyroidism, or exophthalmic goiter, is thus seen to be the product of a vicious circle in which three classes of poisons take part: (1) the *primary causative poison* which excites the thyroid apparatus, (2) the *excess of thyroid hormone,* which provokes excessive catabolism in all tissues, including the cerebrospinal peripheral nervous systems, (3) the *excess of catabolic wastes* derived from all tissues, including the nervous tissues.

PREDISPOSING INFLUENCES.—The fact that a very small proportion of individuals of both sexes exposed to many causes of Graves' disease do not show discernible signs of the malady indicates that some predisposing influence must exist in those who become its victims. That such is the case was well shown during the recent war, by the relatively large number of soldiers reported by Bénard[55] who developed exophthalmic goiter as a complication of *small goiters,* which had previously caused no trouble, after a period of either overwork, intoxication from poor food or water, dysentery, typhoid or paratyphoid, violent emotions, and repeated anxiety. Many other examples of this nature have been published. This accounts for the relative frequency of Graves' disease in goitrous districts, and emphasizes the close connection between the two conditions. So true is this that it is only by tests, which will be described under the heading of Diagnosis (page 239), that some cases of apparently simple goiter can be found to have drifted into the hyperthyroidism class due to some one of the many sources of toxemia which have been enumerated.

In the larger class in which no goiter exists as a starting point the history usually shows that some *disease of childhood,* diphtheria, measles and scarlet fever in particular, has caused focal lesions in the thyroid which, by forming sclerotic areas, have diminished its functional efficiency. The organ, under the stress of some chronic infection or toxemia, is then unable to carry on its functions adequately without becoming inordinately hyperemic—an abnormal process which entails the formation of adventitious vessels and tissues, *i.e.*, the pathological lesions described below as characteristic of hyperthyroidism. In all such cases, therefore, the predisposing influence is acquired thyroid insufficiency. In others, a clear history of *heredity* may be established; Hare[56] observed a case in a girl whose great-grandmother and grandmother suffered from exophthalmic goiter, and whose great-aunt, aunt and mother suffered from goiter. R. G. Curtin[57] reported 40 cases of the disease in fifteen families.

In the cases due to fright or violent emotion the predisposing influence consists in *nervous instability* or neuropathic tendencies, especially hysteria and epilepsy. The relationship with hysteria is well illustrated in the case of a family referred to by Oesterreicher,[58] in which among the 10 children of an hysterical woman there were 8 cases of exophthalmic goiter. One of these had 4 grandchildren, 3 of whom suffered from the disease, while the fourth was hysterical. Some cases of Graves' disease may even show periodicity and be coupled with hysterical or epileptic attacks, as in a case observed by the late Jas. J. Putnam,[59] who states that epilepsy is so closely connected with Graves' disease as to have been thought by some observers to have the same specific symptomatology. We now know, however, that epilepsy as well as Graves' disease is often traceable to a toxemia. The frequency of nervous phenomena in Graves' disease also suggests a neuropathic tendency in a large proportion of cases, particularly those due to emotional stress.

The influence of *sex* is very marked, the great majority of cases occurring in females between the *ages* of *fifteen and forty*. Children are not exempt nor even infants. It is, however, uncommon in old age.

No *race* is wholly exempt. As previously stated, it is relatively most common where simple goiter is endemic, a fact quite in keeping with the frequency with which an apparently benign goiter lapses into a toxic one.

Symptomatology.—Clinical History.—The symptomatic triad: "tachycardia, goiter and exophthalmos," and particularly the term "exophthalmic goiter" have proven exceedingly confusing. Exophthalmos and goiter are not discernible in a large proportion of the cases, and even tachycardia may occur late as a typical sign of the disease, *i.e.*, when accompanied by other signs. Thus, Plummer,[60] on the basis of over 2,900 cases examined at the Mayo Clinic, gives the following order of onset of the most important general symptoms of Graves' disease: cerebral stimulation, vasomotor disturbances of the skin, tremor, mental irritability, tachycardia, loss of strength, cardiac insufficiency, exophthalmos, diarrhea, vomiting, mental depression, jaundice, and death. Out of thirteen main symptoms, tachycardia thus stands fifth, while exophthalmos stands eighth. In cases due to emotional shock, particularly those accompanied by trauma, a tremor, which the patient terms "trembling," may be the first symptom noted; the author has found this to be true in his cases. A clearly-defined goiter often proves, on further examination, to be a case of hyperthyroidism, and a persistent tachycardia, at the time the patient is first seen, usually proves to be due to this condition. But a clear conception of the complete symptomatology of the disease is necessary to establish the identity of many goiterless cases in time to prevent serious damage to the heart, and other advanced phenomena.

Goiter.—The word "goiterless" is used above only in respect to its visual detection, for careful examination practically always reveals some slight swelling of the gland. During deep respiration, deglutition, and coughing, palpation usually reveals a slight cushion-like swelling, provided the palpating fingers are kept motionless over the swollen area; this may be done by resting the thumbs on the manubrium sterni. The swelling usually begins about one-half inch below the upper margin of the thyroid cartilage, which corresponds to the superior border of the isthmus of the gland, and extends downward until within approximately three-quarters of an inch of the upper or jugular notch of the manubrium. Here it slopes gradually, forming a more or less shallow cup with the sternal notch below and the sternocleidomastoid muscles on each side. In some subjects, particularly young women, this cup becomes deeper during menstruation; others show it permanently without suffering from hyperthyroidism. As the goiter develops, it tends in practically all cases to raise the right sternocleidomastoid, slightly distorting this "suprasternal cup"—a new term, but one which clearly depicts the area referred to.

Throwing the head backward while these manipulations are carried out is sometimes helpful; but where the swelling of the gland is only slight, the organ yields readily to the pressure of the overlying tissues, and the swelling may be effaced. It should be remembered also that a normal thyroid gland so fills the depressions of the structures it overlies that it can be traced only with great difficulty, and in some instances not at all.

When a goiter is present, its surface and aspect differ according to the period of development. In many cases, toxic phenomena develop from a so-called benign goiter, either soon or many years after it has developed. Under these circumstances, the goiter presents its original characteristics, being perhaps lobular, hard, irregular in contour, etc., and perhaps causing pressure symptoms such as those reviewed under Goiter (page 204). If, however, the goiter develops as a feature of Graves' disease or hyperthyroidism, it is usually comparatively smooth, soft, evenly diffused, and often compressible. Indeed, as stated by Crotti,[61] "the exophthalmic form of goiter is above all a vascular goiter." It may also bulge somewhat more on the right side than on the left.

Vasodilatation.—Both symptomatically and pathogenically this is one of the most important features of the disease. It occurs no matter what the origin of the hyperthyroidism may be, and as a result of the catabolism which the latter induces in the muscularis of the blood-vessels. An additional factor probably takes part in the process. Twelve years ago the writer[62] emphasized the fact that the thyroid secretion carried out its functions by sensitizing (as opsonin) all cells, including pathogenic organisms and the nervous system. An excess of thyroid gland, therefore, by oversensitizing the depressor nerve, causes it to exercise its functional prerogative, which consists in causing general vasodilatation. This action of the thyroid hormone was also noted by Asher and Flack.

While causing general vasodilatation, the thyroid gland is itself influenced by it, all its vessels being so dilated that, if the goiter is compressed evenly with the hand, it may recede as would a sponge, filling out again when the pressure is released. Pulsative expansion may also be detected by palpation, and may be sufficient at times to be visible. Stethoscopic auscultation elicits a whirring sound, differing from the hum that appears in the neighboring veins when these are compressed. The important pathogenic feature in this connection is that, as shown by Claude Bernard, the increased flow of arterial blood through the thyroid apparatus, due to the dilatation of its vessels, is the cause of augmented functional activity, as is the case with all other structures which receive an excess of arterial blood.

If, while the whirring sound in the thyroid is heard stethoscopically, the pulse is felt simultaneously, it may be found that the sounds are synchronous, particularly if the larger portion of the gland is auscultated; with due care the sound may often be traced over the course of the thyroid artery to the carotid, the pulsations of which are normally expansile. A rhythmic murmur, synchronous with the pulse, may also be heard over the eyeball, as pointed out by Riesman.[63]

These expansile pulsations are common to all large arteries, including those of the abdomen, and may be augmented by the ingestion of much liquid food. The size of the thyroid is also thereby increased. The veins—the jugulars in particular—may also stand out prominently, those of the retina sometimes appearing enlarged and tortuous. Hyperplasia of various lymphatic organs, especially the thymus and spleen, is also commonly observed.

We are not dealing here with increased arterial tension, for the rapid pulse peculiar to the disease is soft, of small volume, and at times dicrotic, the blood-pressure being usually quite low, sometimes below 100, unless some concurrent disease is present. The vascular torpor incident upon vasodilatation is such in some cases as to give rise to edema early in the course of the disease; this has erroneously been attributed to concomitant myxedema. This edema may be localized in the eyelids, the face, the extremities, as "puffy swellings"; it is in fact often fleeting, and is also aggravated rather than improved by thyroid medication.

Course of the Disease.—*Transition Stage.*—At a certain time in the history of each case, improvement asserts itself. Although slight at first, it finally becomes so marked that the patient concludes that he is approaching full recovery. The tachycardia lessens, the tremors, irritability, emotionalism, heat flushes, all tend to disappear, the emaciation seems to be replaced by a relative embonpoint, the flattened breasts fill out, and even the goiter seems to have receded, at least irregularly.

Careful examination of the goiter, however, reveals a peculiar fact. It is no longer as compressible as it was formerly, and here and there palpation will reveal nodular masses. The whirring sound in the gland is hardly audible under stethoscopic auscultation. On the whole, the character of the gland has changed. Briefly, sclerotic areas are steadily developing in it, and connective tissue is gradually replacing the functional elements. There finally comes a time when the cirrhotic changes have progressed sufficiently not only to reduce the secretion of the gland to normal—when the improvement and period of fictitious recovery ensues—but to steadily decrease it until *hyperthyroidism* is replaced by *hypothyroidism,* and then by marked myxedema.

Myxedematous Stage.—It has been stated that myxedema occurs in conjunction with hyperthyroidism. In reality, at a given time in an advanced case, certain symptoms of myxedema appear before those of Graves' disease have completely disappeared. Again, the early edema of the latter, which does not yield to thyroid gland medication, the loss of hair, and other symptoms due to the catabolic action of the excessive thyroid secretion, are sometimes mistaken for those of myxedema. But when the latter really occurs its symptoms are unmistakable; as we shall see presently, they include hypothermia, sensation of coldness, obesity with non-pitting rough dry skin, the formation of suprascapular swellings or pads, alopecia or coarse hair, and mental torpor—all differing totally from the symptom-complex of hyperthyroidism.

Myxedema as the terminal stage of Graves' disease is far more severe than in the primary form, owing to the fact that it seizes upon an organism already worn out by the former disease. If the patient does not become the prey of an intercurrent disease, he lapses into a profound cachexia, with increasing cardiac weakness, mental torpor, alternating with periods of insanity of a degenerative type, soon followed by fainting spells and heart-failure, which is the usual mode of death.

PHYSICAL FINDINGS.—*Eliminatory System.*—In the less severe cases the skin shows only symptoms indicating that the terminal arterioles which admit blood into the cutaneous capillaries are dilated. Telangiectasis is occasionally observed, and dermographia is common, the red line being readily brought out by rubbing a pencil over the skin. The dilatation of the capillaries accounts also for the sensation of superficial heat and sweating which is experienced, the cutaneous capillaries receiving an unusual volume of blood, and for the "flushes," which are only exacerbations of the cutaneous hyperemia appearing when any intercurrent cause brings about a temporary rise in blood-pressure. The same hyperemia evidently affects the mucous membranes likewise, as evidenced by the redness of the conjunctiva, the epistaxis, and other hemorrhages occasionally observed.

In severe cases, another factor enters into play, that of toxic wastes formed as a result of a widespread, very active, breaking down of the tissues. These wastes accumulate in the circulation, imposing upon the eliminatory functions, intestinal, renal and cutaneous, already subjected to inordinate activity, considerable additional work. This doubtless contributes to the stubborn diarrhea witnessed in these cases; polyuria, *i.e.*, frequent urination, is also a common symptom. The skin with its sweat-glands, already subjected to stress by frequent exacerbations of sweating, is scarcely able to carry on its eliminatory functions, and even to bear without reaction the presence of an excessive amount of wastes. Hence the occurrence of one or more disorders: severe pruritus, erythema, acne, urticaria, sclerodermia, leukodermia, vitiligo, etc. The pilous system being also involved, there is loss of hair, beginning often at the forehead and spreading backward, and in many cases affecting the lashes and outer half of the eyebrows, the axillæ, pubis, etc. The nails also show signs of perverted nutrition, evidenced by a tendency to brittleness and onychia.

Cerebrospinal System.—The morbid nervous phenomena are due, as we have seen, not only to excessive catabolism of the fatty components of the nerve-cells, but also to the passive hyperemia caused by the general vasodilatation previously referred to. The entire cerebrospinal and the peripheral nervous systems receive an excess of abnormally active blood, and are thus subjected to the morbid effects of the disease. Hence the fact that cerebral excitement, registered by Plummer as the first sign witnessed, followed closely by mental irritability, are familiar symptoms. Emotionalism, the early emotional tremor of fright, the excitability, tending to lapse into anger or outbursts of passion, the unnatural vivacity, capriciousness and restlessness, the congestive headaches, tinnitus, and insomnia are all its normal consequences. It is self-evident that the cerebral hyperemia may assume greater proportions and cause acute delirium, hysterical outbursts in predisposed women, and even epileptoid paroxysms—which, according to Putnam, have been thought by some, owing to their frequency, to belong to the specific symptomatology of Graves' disease.

The spinal hyperemia and hypercatabolism account for the tremor and exaggerated reflexes observed early in the history of these cases, and for the tingling in the extremities alternating with numbness, which is in itself indicative of vascular spasticity of central origin; the latter shows itself also by areas of hyperesthesia, and by sudden and rapidly succeeding flushing and paling of the face and upper thorax, which coincides with a very low blood-pressure, as noted by Harlow Brooks. A contributing factor is probably the presence in the blood of waste products of catabolism due to the excessive thyroid activity.

Muscular System and General Metabolism.—That the thyroid gland promotes catabolism has been emphasized recently by Plummer's[64] statement that "the thyroid hormone is fundamentally a part of the catabolic process of higher animal life." It is shown by the rise of temperature which frequently occurs in these cases. But of signal importance in this connection is the excessive loss of weight observed in hyperthyroidism, which may reach one hundred pounds or more in a few weeks or months in severe cases, exceeding even cancer in its ravages.

This phenomenon is accompanied by excessive excretion of urea and phosphoric acid, with abnormal oxygen intake and carbon dioxid output, and, commonly, glycosuria. That an attempt is made to compensate for the intense breaking-down of tissue is shown by the ravenous appetite and thirst, but, although this serves to delay the issue, albumins, fats and carbohydrates are steadily consumed to a degree exceeding the compensatory intake, with cachexia as a result.

Myasthenia or muscular weakness, fatigue, giving way of the knees, general lassitude, etc., are usual results of the excessive catabolism, both in the muscular elements themselves and in their nervous elements, the motor impulses of the latter being weakened owing to the abnormal destruction of the functional constituents.

The principal symptom of the disease, tachycardia, which persists even during sleep, is also due to the irritation of the sympathetic nervous system. Louis B. Wilson[65] has found that toxins injected into the superior cervical ganglion were capable of producing various symptoms of exophthalmic goiter. If this is true insofar as the actual pathogenesis of the disease is concerned, it would further emphasize the importance of the primary toxins as causative factors. The catabolic impairment of the fatty bodies of the nerve-cells by the thyroid hormone, and a similar action exerted upon the vascular muscularis, afford a more logical explanation of the ubiquitous vasodilatation which represents the most important factor of tachycardia. The coronaries, dilated and abnormally expansile, allow an excess of arterial blood to enter the myocardium, and its inherent reaction, contractility, is increased, to compensate, by an increase in the number of beats—reaching in some cases as much as 200 per minute—for the loss of *vis a tergo* motion resulting from the vasodilatation.

The pounding of the heart against the chest-wall, sufficient at times to shake the whole chest and to be heard at a distance, which is aggravated by any degree of exertion, and is especially marked when lying down, the nocturnal attacks of *pseudo* angina pectoris occasionally witnessed, often so severe as to threaten life, all find their logical explanation in the myocardial flood of arterial blood. The irritability, irregular palpitations, and functional murmurs, are only secondary symptoms of the myocardial hyperemia, since they disappear when, through appropriate treatment, the excessive secretory thyroid activity is controlled.

We have seen that the excessive catabolism in the body at large indicates more or less rapid emaciation. The same morbid process prevails in the heart-muscle, and the result is similar to that in the skeletal muscles: increasing weakness, with little change. The result is the familiar gradual dilatation. The heart becomes so large in some instances as to cause displacement, the apex-beat, as in a case under the writer's observation, being close to the medial line of the thorax. Here again we have only an artificial dilatation, so to speak, for if the organ is examined roentgenographically during treatment, its walls will be found to recede gradually as the patient improves.

(*a*) ***Tremor.***—The metabolic stress to which the muscular elements are subjected brings about contractile instability, owing to the debilitating effects of the exaggerated metabolism. The muscular elements being held in leash between extension and contraction, tremor is the result of loss of equipoise between the two sets of antagonistic muscles involved. It is particularly observed when the arm is stretched out and the fingers are in extension, and by standing behind the patient and placing one's hands on his shoulders one may feel his whole body tremble, in well-marked cases. Fatigue increases the tremor, while conversely it is reduced when the patient is in repose in the recumbent position. It is highly benefited by absolute rest.

(*b*) *Paralyses.*—These are normal results of excessive catabolism in the muscles and nerves, the central nuclei of the latter showing chromatolysis in some instances. They may be transient or permanent, and show a predilection for the muscles of the face, eyes, palate and larynx, the voice either assuming a high pitch or becoming tremulous. Muscular atrophy of a spinal type may affect the extremities, the muscles of the hands in particular. Muscular cramps, local spasms, and jerking movements are also noted.

Alimentary Tract.—Excessive metabolism in the gastric mucous membrane causes abnormal secretory activity, manifested by gastrosuccorrhea with hyperchlorhydria. This in itself excites the desire for food during and between meals, and gives rise to various gastric disturbances: pyrosis, dyspepsia, aërophagia, etc.; these are fitful and apt to occur in the morning, the gastric fluids having accumulated during the night. The gastric muscular coat, being also the seat of excessive cellular interchanges, is irritable, and contracts readily, thus contributing to the frequent attacks of vomiting, which in some cases become sufficiently severe and frequent to prove threatening. The spasticity of the muscular coat and the hyperchlorhydria, aided perhaps by the spinal hyperemia, together provoke gastric crises, which have been compared to those observed in tabes.

The intestines are affected in the same way; hence the persistent diarrhea, which represents here what the gastrorrhea is to the stomach. The intestinal mucosa and its glands are stimulated to excessive secretory activity, producing serous stools poor in bile, and therefore colorless or even greyish, although the volume of bile secreted is normal or excessive. The muscular coat of the intestinal canal being likewise over-supplied with blood, peristaltic activity is also stimulated, sufficiently in some instances to cause marked discomfort, which is increased by the flatulence common in such cases. All these phenomena, gastric and intestinal, disappear as soon as the hyperthyroidism is overcome.

Ophthalmic System.—Having now ascertained that all the morbid phenomena of the disease may be attributed to passive vasodilatation, mainly of catabolic origin, we find a ready explanation for the pathogenesis of *exophthalmos.* Briefly, this symptom, which usually occurs late, is due, in the writer's opinion, to some degree of infiltration, doubtless of blood-plasma, into the retrobulbar connective tissue, a form of edema capable of fluctuating with the variations of the general vascular tension. Pathologists have failed to find edema postmortem, but they overlook the fact that the peripheral structures are drained of their fluids as death approaches; these accumulate mainly in the splanchnic area. This infiltration of plasma behind the eye accounts for the liability of exophthalmos to undergo rapid variation, for its prompt development in some instances, and for the opposite effect in others, and also for its early recurrence after operation, unless vasoconstrictors are administered. It accounts likewise for the persistence of this symptom after operation when the plasma undergoes organization.

Yet, this alone does not explain the unilateral exophthalmos occasionally witnessed. This phase of the problem is accounted for, however, by the facts that (1) the cervical sympathetic system controls the postorbital circulation, and (2) that chromatolysis of any of the cervical ganglia, from any cause, or pressure upon the cervical sympathetic nerve anywhere along its course, impairs its efficiency for the transmission of impulses. Hence the fact that we occasionally witness an exophthalmic eye on the same side as the greatest enlargement of a goiter, owing to pressure upon the cervical sympathetic nerve. When the opposite condition is the case, chromatolysis of the cervical ganglia of the side opposite to that of the larger goitrous mass, by impairing the conductivity of impulses to the postorbital arterioles of the affected eye, permits their relaxation even beyond that to which all systemic arteries are subjected.

In some cases, exophthalmos assumes such proportions that the eye is imperfectly kept moist, or is not kept moist at all, by the lids, and therefore becomes ulcerated; conjunctivitis, keratitis and necrosis of the cornea occur in rapid succession. The organ may even be forced out of its orbit and undergo destruction.

In many cases a stare is observed, which should be distinguished from exophthalmos, although it frequently coincides with it. This stare is probably caused by more or less prolonged spastic contraction—due to hyperemia of the eye-muscles—of the non-striated fibers which aid in separating the eyelids widely, as in ordinary staring. Various signs have been elaborated from a similar spasticity of the same ocular or palpebral muscles:

(1) Infrequent winking.

(2) Stellwag's sign—the patient winking once or twice a minute or even less often, instead of the usual fifteen or twenty times.

(3) Lagging of the upper lid.

(4) Graefe's sign. When the patient looks down without lowering his head, the lid sometimes ceases to descend at once.

(5) Spasm of the upper lid.

(6) Kocher's sign, the eye being turned up, when the patient watches a moving finger.

(7) Boston's sign, the eye turning downward when the patient follows the finger as it is moved up or down. The lid, during its excursion, shows a slight spasm, after which it proceeds on its course.

(8) Excessively large palpebral fissure.

(9) Dalrymple's sign, the eyelids being far apart, and the condition differing from exophthalmos in that the eye is not pushed out.

(10) Impairment of converging power (Möbius' sign), revealed when the patient, asked to follow a pencil that is gradually approaching his nose, is unable to follow it with both eyes when it comes near his face.

(11) Paralysis of the external recti. This has sometimes, although rarely, been observed.

While impairment of the vascular supply of all the muscular structures involved plays a large part in the morbid process, the nervous supply, which is also functionally impaired, doubtless contributes its share.

Sexual System.—The virtual loss of sexual appetite is explained by the debilitating influence of persistent catabolism in the generative organs. Menstruation may become scanty or cease altogether. Premature menopause in young women is not uncommon, the general trend of the organs of generation being that of all others, *viz.*, toward atrophy. Yet, when the degenerative process has not exceeded a certain limit, all functions are gradually restored, if the thyroid hypersecretion is adequately controlled.

Blood.—A peculiarity of Graves' disease is the presence of lymphocytes in unusual numbers in the blood, especially in young subjects and in adults when, as is sometimes the case, the thymus is persistent.

From the writer's viewpoint, the latter organ is the source of cells resembling lymphocytes—thymocytes—which, during the process of growth, supply the nervous and osseous systems with nucleins. It is possible, therefore, that the purpose of the lymphocytosis is to replace the phosphorus-laden myelin of nerves and ganglia which undergo active catabolism. Or it may be merely the result of the active metabolism to which the thymus is subjected by the excess of blood circulating through it. Kocher, who called attention to this phenomenon, also found the number of leukocytes greatly reduced, the neutrophils in particular. The coagulating power of the blood is also reduced in severe cases.

Diagnosis.—By the time a case of hyperthyroidism or Graves' disease reaches the physician the symptoms are such as to render a diagnosis quite easy. And yet, it has been the writer's misfortune to see advanced cases that had passed through the hands of several physicians —in one instance fifteen—without being recognized. In every instance in which a goiter was not a prominent feature, the tachycardia had attracted attention to the heart, and either digitalis, which did more harm than good in the sthenic stage, or nitroglycerin, which did harm in all stages, had been ordered.

Tachycardia then must be regarded as a misleading symptom unless all other symptoms of the case, and its history, are carefully looked into and analyzed. Particularly is this necessary in view of the fact that various symptoms, the lustrous eyes, the nocturnal "palpitations," suffusion of the face, diarrhea, occurring without cardiovascular murmurs, and edema, may also accompany a disorder of the heart. Finally, as we shall see, tachycardia may also suggest neurasthenia.

Emaciation is another misleading sign unless the symptom-complex of the case is carefully studied. It progresses very rapidly in some cases, and may simulate some forms of advanced internal cancer, in which cachexia has just started. Such cases also show a weak and rapid pulse, night sweats, insomnia, and, at times, where a defensive febrile process is active, lustrous eyes and a warm skin. Soon, however, the typical signs of the cancerous cachexia—in which the patient's face is sallow and sunken, and the conjunctivæ pearly—reveals itself, thus eliminating all doubt. The febrile process and other symptoms which have been enumerated, preceding the advanced cachexia, may also suggest tuberculosis or typhoid fever. However, doubt on this score is soon eliminated by physical and laboratory methods of diagnosis. Tuberculin should not be used if hyperthyroidism is suspected, as sufferers from this disorder are extremely sensitive to its toxic effects.

The marked fatigue attending any effort, mental or physical, may suggest neurasthenia. Particularly is this the case when this disorder includes "nervousness," transitory heat flashes or "vasomotor storms," hysterical manifestations, throbbing of the arteries, including the aorta and carotids, vertigo, tremor, loss of weight and even tachycardia. But the latter is not constant, as in Graves' disease. Nor is the asthenia in the latter ever so marked in neurasthenia; moreover, it is accompanied by exuberance of disposition, and a good appetite. An effort will be confidently undertaken, but dropped through inability to carry it out. Briefly, the activity of excessive metabolism is followed by the collapse associated with its consequence: exaggerated catabolism.

Tests for Hyperthyroidism.—When a goitrous enlargement is present and the leading symptoms of hyperthyroidism, especially tachycardia, asthenia, tremor, throbbing arteries and lustrous prominent eyes, are also present, a diagnostic error is scarcely possible. When, however, the goiter is not accompanied by systemic symptoms, it becomes a question, when treatment is begun, whether the gland may not be on the threshold of a toxic phase since, in that case, the general measures indicated would be quite different. An increase in the number of polynuclears and lymphocytes has been suggested as indicating hyperthyroidism, but as the causes of benign goiter already reviewed produce similar effects, the value of this phenomenon as a test is negative.

The simplest test is tentatively to administer thyroid gland. If larval hyperthyroidism is present, a sudden outbreak of typical symptoms will occur, while if the goiter is benign, no such symptoms will appear; in fact, reduction of the goiter may follow, owing to the antitoxic action of the thyroid. However, this is not always a safe procedure, as the use of even a small quantity of thyroid may act as a match to gunpowder and start a conflagration which it may prove difficult to arrest.

The adrenalin tests are greatly to be preferred. The best of these is that of E. Goetsch.[66] He based his method upon the fact that a patient suffering from hyperthyroidism is hypersensitive to adrenalin. A hypodermic syringe with a fine needle is used to inject 0.5 c.c. (8 minims) of a 1:1000 solution of adrenalin into the deltoid region, subcutaneously. The positive reaction is characterized by an early rise in blood-pressure and by a pulse-rate varying from 10 to 50 and normally proportional to the degree of thyroid intoxication present. Symptoms such as asthenia, tremor, throbbing, vasomotor changes, apprehension and nervousness may also occur. These characterize a mild case or represent an increase of the symptoms which are already present.

Another test was proposed by Loewi[67] on the ground that in hyperthyroidism the sympathetic nervous system is abnormally irritable, and that the dilator fibers of the iris, governed by the sympathetic system, respond abnormally to adrenalin. Therefore, by instilling a 1:1000 solution of adrenalin into the eye, dilatation of the pupil may be produced if hyperthyroidism is present. This test has been confirmed by a number of observers.

Basal metabolism, which means the heat production of the body measured twelve or more hours after taking food, *i.e.*, before breakfast, and during complete muscular rest, is used as a test in many diseases. The greatest variations noted, however, occur in diseases of the thyroid apparatus, ranging from double or more than the normal ratio in hyperthyroidia, to one-half or more of the normal in hypothyroidia. While either plus or minus rates are not necessarily pathognomonic of the existence of actual disease of the thyroid apparatus, they afford valuable testimony in favor of such a condition when present in conjunction with other symptoms. Again, fluctuations in rate make it possible to follow closely the progress of a given case during treatment. Additional details upon the subject will be found on page 211 of the second volume of the present work.

Complications.—THE THYMUS AS A COMPLICATING FACTOR.—Persistent thymus is a source of considerable danger in Graves' disease when operative procedures are resorted to. It may cause death during the operation, several days after it, or even in the midst of convalescence. Although such surgeons as Halsted and Kocher only regard this concurrence as exceptional—4 per cent., in 500 cases, according to the former—others find the proportion much larger: over 76 per cent. of 133 patients who died after a thyroid operation. According to Capelle the proportion is 95 per cent.

In considering any form of operation, therefore, even ligation of the arteries, the condition of the thymus should always be determined by *x*-ray examination and other diagnostic measures indicated in the article on the gland (page 165). Such cases are apt, unfortunately, to appear in a mild form, with slight exophthalmos, moderate tachycardia, and a small goiter. Halsted describes a peculiar grayish, bronze-hued skin. The writer has not been able to confirm this observation.

There is, however, a tendency to dyspnea, due doubtless to pressure on the trachea, which is not accounted for by the small goiter.

There is also a painless dysphagia, with a sensation which the patient ascribes to "a lump deep down in the throat," also occasionally enlargement of the superficial veins. The writer has noticed, in some of these cases, besides the typical thymic dullness over the manubrium sterni, an unusual tendency to hacking cough, sufficient in one instance, in conjunction with the warm skin and mild tachycardia, to suggest pulmonary tuberculosis. He also noted aggravation of all pressure symptoms when the patient partook of a hearty meal. None of these symptoms are pathognomonic, however; when present, they merely suggest the necessity of exceptional care. We have seen, however, that lymphocytosis is often observed in Graves' disease, and that the thymus supplies the blood with these cells. If added to the other symptoms described, we find lymphocytosis, the presence of persistent thymus is practically certain.

When death occurs in these cases it is probably due, as in status thymolymphaticus, to pressure of the thymus upon the trachea or other neighboring vital structures. Whether immediately after the operation or later, the patient usually begins to gasp for breath, becomes violently excited and cyanotic, then lapses into unconsciousness and death. Why this should be caused by the enlarged thymus after removal of the thyroid is still obscure; but if we recall the antitoxic functions of the organ and the fact that the thymic lymphocytes, or thymocytes, are rich in nucleins which are themselves rich in phosphorus, the possibility suggested by the writer is worth investigating. He considers that we are dealing with a nucleic acid or phosphoric acid toxemia, which in turn markedly raises the blood-pressure, increasing the volume of the gland and its pressure upon surrounding tissues. At any rate, this phase of the problem is obscure, and, if a surgical procedure is inevitable, it is best to follow Crotti's advice, *i.e.*, to avoid the danger by removing the thymus with the part of the thyroid which is sacrificed.

Treatment.—The first step in the treatment of hyperthyroidism or exophthalmic goiter, if a successful result is to be attained, is the *abandonment of empirical methods,* and particularly of symptomatic treatment, which often leads to the use of agents which tend to aggravate the morbid process and to impose upon the patient untimely burdens. Rest, for instance, acts as a powerful adjuvant by reducing the metabolic rate; if a poison from any source is keeping up the thyroid toxicosis, rest, a ruinous luxury to many, will not materially affect the morbid process, and may perhaps occasion the patient considerable harmful anxiety. Again, before any treatment is instituted, one must consider the two general classes into which the cases met with are divided as regards their primary pathogenic cause, the toxemic and the neurotic. Measures indicated in one group may fail in the other.

TOXEMIC GROUP.—This includes the cases of hyperthyroidism most frequently encountered in practice. Many of them do not show thyroid enlargement. Some cases, in which the condition is often mistaken for neurasthenia, may be due to excessive fatigue, as a result of cerebral or physical exhaustion. This term is to be taken in its relative sense only, for it may apply to a young girl entrusted with physical or mental work beyond her powers of endurance as well as to a strong soldier exposed to the rigors of a campaign or to exhausting marches. Major W. Johnson[68] has described many such cases in which even exophthalmos was produced. Rest alone, if sufficiently prolonged, sometimes suffices in such cases, provided nourishing food is available, inappropriate drugs are avoided, and the patient does not resume an occupation demanding effort exceeding the limits of his strength. The tachycardia, caused by the exacerbation of thyroid activity calculated to break down accumulated toxic wastes, gradually subsides, and the patient is restored to health, although his thyroid gland remains sensitive. In the majority of cases, however, the condition persists, particularly if there is a history of goiter or kindred disorders in the patient's family. In all such cases, **arsenic,** or other measures indicated in the more severe cases, and described below, are necessary.

The milder cases also include those in which the goiter may be hardly discernible, small or quite evident, and due to fecal intoxication or to coprostasis. By repeated *x*-ray examinations, or with the fluoroscope, in such cases, a barium meal may sometimes be found to be delayed for two or more days in the intestinal canal, and in most instances in the cecal area. Under such conditions toxins are produced in large quantities through the development of bacilli of the colon group in the protein dejecta. These toxins, in turn, by provoking a violent defensive activity of the thyroid apparatus, cause it to secrete to excess, thus evoking the general phenomena of hyperthyroidism or exophthalmic goiter. The treatment should, therefore, be directed toward ridding the intestine of the fecal stasis, and preventing its recurrence. Active **purgation** is indicated, followed by a cleansing **enema,** and high colonic **irrigation** with a solution of **sodium chlorid** and **sodium bicarbonate,** one teaspoonful of each to a pint of warm (108° F. or 42.22° C.) water. The solution may be brought into contact with the entire colon by having the patient lie face downward with the buttocks raised, as for a rectal examination, and then having him, while the rectum is filled with one quart of the solution, turn gently on his right side and remain there for at least twenty minutes. The weight of the fluid causes it to gravitate toward the cecum, to straighten out ptoses and kinks and detach masses that tend to adhere. To sustain intestinal activity, **sodium phosphate,** one teaspoonful in a glassful of hot water on rising and retiring, is the most satisfactory agent. The intestinal lavage should be practiced once or twice a week, until another *x*-ray or fluoroscopic examination indicates adequate functional activity of the whole tract.

In some instances spasmophilia may result from the accompanying excessive adrenal activity and the resulting hypermetabolism. It favors cecal stasis by causing spasm of the ring of Cannon in the intestinal musculature and also retention of the rectal contents through tonic constriction of the sphincter muscle. This contribution to the vicious circle constituting the disease is soon eliminated by removing the original cause of the toxemia—in the present instance the coprostasis. If it is not relieved, however, **calcium lactate**, 5 grains (0.324 gram) three times a day, will counteract this annoying symptom.

To perpetuate the benefit obtained from the intestinal treatment, two important additional measures must be insisted upon, *viz.*, a **diet** which will not cause a recurrence of the coprostasis, and adequate **rest.**

As to the diet, Falta found that proteins cause increased activity of the thyroid, and Rudinger's findings showed that a diet practically free from proteins and rich in carbohydrates tended in the opposite direction. These facts account for the benefit resulting from complete abstention from butcher meats and from restriction to a vegetable diet in addition to bread *ad libitum*, and fruit, with white-meated fowl, fish, and milk as mainstays. Milk half diluted with Vichy forms an excellent beverage, which tends to counteract the acidosis resulting from the excessive metabolism. This regimen is not necessary when the toxicosis is of intestinal origin, but it is essential in every case of hyperthyroidism, whatever its cause may be.

If the digestion is poor, with pyrosis or hyperchlorhydria, a common result of hyperthyroidism, lavage is indicated, and is invariably beneficial for the local as well as the systemic disorder.

Absolute rest is of the greatest importance, owing to the fact that it reduces to a minimum the production of tissue wastes of muscular origin and also the strain on the heart. **Mental rest** is no less essential, since cerebral activity is also attended by the production of wastes which, like those derived from other tissues, sustain the morbid activity of the thyroid. Whatever the cause of the pathogenic toxemia may be, whether intestinal, tonsillar, nervous, etc., the thyroid, or rather its governing center, becomes hypersensitive, and thus finds in physical and mental work a source of morbid stimulation which may perpetuate the disease independently once it is started. This, as we have seen, may take place even in the milder cases.

The next most frequent causes in the writer's experience have been diseased teeth, gums, or tonsils. These pathogenic groups are considered together because suggestive evidence is available to show that an organism common to these structures is the source of the pathogenic toxin. Thus, while the *Entameba gingivalis* of Gros is the pathogenic organism of pyorrhea alveolaris, Evans, Middleton and Allen J. Smith[69] found that in 362 goitrous individuals, 90 per cent. of whom had nasal and tonsillar infections, 97 per cent. of the 34 cases in which the tonsils were examined microscopically showed *Entameba gingivalis* in the tonsillar crypts. Of the 16 patients of this group who were given **emetin hydrochlorid,** 12 no longer showed entamebæ in the crypt contents, while in 23 cases similarly treated, a reduction in the bulk of the goiter occurred in 18, with marked improvement in 4 cases of exophthalmic goiter. While this suggests that emetin hydrochlorid (from 1/8 to 1/2 grain, or 0.0081 to 0.0324 gram) might be tried in those cases in which surgical measures or extraction of teeth cannot be carried out, the fact remains that permanent results can only be secured by radical treatment: **extraction of the affected teeth** if they are shown by *x*-ray examination to be abscessed, and the **removal of the tonsils.** No measure available at the present time renders certain the absence of small hidden foci, which may at any moment cause a relapse. The fact that, as stated by Beebe, repeated attacks of acute tonsillitis appear in the history of from 35 to 40 per cent. of the cases of hyperthyroidism in subjects from sixteen to twenty-four years of age illustrates the importance of this cause.

More accurate diagnosis is possible by means of *x*-ray examinations of the teeth, but the aid of a dentist who gives considerable attention to this class of cases is necessary, since the peridental membrane may be sufficiently diseased to cause general infection without causing local lesions discernible by roentgenoscopy. In a case under the writer's observation local measures on the part of a competent dental operator sufficed to bring about recovery. Tartar, carious teeth, or even bridges, plates, or any abnormal state entailing abrasions of the gums or of the peridental tissues demand attention as soon as possible.

Next in the order of frequency are disorders of the nasopharynx, sinuses and lingual tonsil. Of the nasopharyngeal disorders, adenoid vegetations are the most frequent in young subjects. Removal is of course indicated in such cases. In some instances the tonsils are diseased simultaneously, and occasionally the upper sinuses likewise. Thorough treatment of these disorders by specialists is imperative if a satisfactory result is to be obtained.

Pregnancy and parturition, irrespective of cases in which the disease existed previously, are not infrequent causes, owing mainly to the increase of toxic wastes transferred by the fetus to the maternal blood. Here we must depart from the usual path, for the excessive activity of the gland is compensatory; acting normally it would be incapable of successfully opposing the toxemia. In those cases, the results of tentative doses of thyroid gland often show that by assisting the gland one may bring about the gradual disappearance of the morbid hyperthyroidism, and that it fails to return once the cause of the toxemia is eliminated. Where the hyperthyroidism persists after parturition, it may be mistaken for puerperal septicemia and may even cause puerperal eclampsia. Absolute **rest** on the back, **hypodermoclysis,** small doses of **thyroid** and **adrenalin** if the heart is feeble, soon prove beneficial, and lead to recovery if the diagnosis is correct. In those cases in which the disease existed prior to conception the symptoms often improve and may even disappear after parturition. If the tachycardia persists, however, the indications are similar to those for ordinary cases. When, however, pregnancy brings on acute symptoms, which rapidly become worse, **premature labor** should be induced.

Acute diseases, typhoid fever, scarlet fever, influenza, diphtheria, etc., bring on hyperthyroidism in practically every instance, as is readily shown in some instances by palpation, and in the majority of cases by hyperesthesia of the gland itself, irrespective of the superficial hyperesthesia, as recently shown by Lian. As we have seen, however, local lesions such as focal hemorrhages or necrosis may occur; in other cases true thyroiditis develops. In the vast majority of cases, uncomplicated hyperthyroidism persists as a feature of convalescence, taking part in the destruction, or preparation for elimination, of wastes and detritus formed during the acute process. In rare cases, true exophthalmic goiter results. Chronic disorders, such as syphilis and tuberculosis, may also induce the disease by promoting a prolonged defensive reaction on the part of the organ. Here the **specific treatment of the causative disease** usually suffices to arrest the hyperthyroidism.

NEUROGENIC GROUP.—In reality this group, although due to emotional stress, fright, violent emotion, grief, or anger, is closely allied to the toxemic group, since the effect on the nervous system is such as to cause it to excrete into the blood toxic wastes—neurin in particular—which, like all other poisons, provoke an excessive reaction on the part of the thyroid. We have seen that the thyroid hormone further damages the nervous system in such cases by breaking down systemic fats, the fatty bodies, myelin, etc., which all nerves and their cell-bodies contain. The best results are obtained in such cases by measures which tend to give the shocked central neurons an opportunity to resume their normal histological structure: **absolute mental and physical rest,** in order to reduce to a minimum the production of wastes of cerebral and muscular origin.

Another important factor in these as in other toxic cases is the **diet.** Thyroidectomized dogs suffer severely when fed on meats; they recover when fed on milk; carnivora in general suffer seriously, herbivora least from the same operation. Obviously, the thyroid must contribute to the breaking down of meat proteins. Indeed, as stated above, while Falta found that proteins increase the activity of the thyroid, Rudinger observed that a diet free from proteins and rich in carbohydrates tended to decrease it. Our aim being to inhibit thyroid activity, we should prohibit all meats, fowl, fish, even oysters, and feed the patient only on milk and its various products, butter, cheese, cream, buttermilk, vegetables and ripe fruits, watching out for acidosis by testing the saliva with litmus, and using freely as a beverage imported **Vichy** (Celestin) in order to neutralize with its sodium bicarbonate what phosphoric acid the blood may contain—another source of thyroid excitation—and also to protect the kidneys.

An important factor in this connection is the fact that the intestines, owing to the nervous disturbances, may fail to carry on their functions, thus causing, in these neurogenic cases, a retention of fecal matter which itself may, through the production of toxins by colon bacillus colonies, provoke considerable thyroid reaction. A **saline purgative,** preferably **sodium sulphate (not calomel,** which is a thyroid stimulant), followed, if need be, by **sodium phosphate,** a teaspoonful in a glassful of hot water each morning to prevent constipation, will usually suffice to eliminate this fourth source of thyroid excitation.

A neurogenic case, treated soon after the emotional stress in this manner and without drugs, will usually respond satisfactorily, even though the tachycardia is marked—130 or more. The pulse steadily goes down to normal and, when the vicious circle is broken, often remains so. But the fire is readily kindled anew. In one of the author's cases, after the pulse had been 84 for nearly two months, a short dance promptly caused it to jump to 130 and to stay there, thus necessitating a resumption of the rest, dietetic measures, etc. This indicates that the thyroid remains hypersensitive for several months after such an experience, and that adequate precautions are in order during that period.

It is an unfortunate fact, however, that cases of hyperthyroidism of any kind seldom reach the endocrinologist early. In most instances, the patient has run the gauntlet of various diagnoses, often of neurasthenia or of some undefined heart disease, and has been given tonics (also digitalis) which do more harm than good, while the loss of weight, the hot skin, and sweating may have suggested either internal cancer, tuberculosis, or even typhoid fever. Medication given for these conditions may fit the diagnosis, but not the patient. When, however, enlargement of the thyroid, which occurs only in about one-fourth of all cases, becomes sufficiently marked to be clearly perceived, this sign, plus the tachycardia, suggest the harmful "symptomatic" treatment, which is then persisted in for a long time. This failing, the surgeon is recommended. Another source of delay is thus inaugurated, the operative risk, the scar, the possible after-effects, etc., acting as deterring factors. Finally, when it has become a question of life or death, surgical measures are performed, after the case has become a poor operative risk or one difficult to handle by the endocrinologist—meaning by this term a general practitioner who knows enough of endocrinology to treat cases intelligently.

By this time, the measures previously described, although quite as important as before, no longer suffice. Another source of toxemia has entered upon the scene, to aid the toxins previously mentioned in destroying the patient. This factor is an extension, so to speak, of the excessive catabolic action of the thyroid hormone, when the protective activity of the organ becomes so aggressive that it begins to break down, besides the systemic fats, the albumins, and various tissue-cells of the body at large. When this occurs, the loss of weight of the patient is sometimes astounding—122 pounds in eleven weeks in one of Schlessinger's cases, 47 pounds in a few days in one reported by Funke. Some patients literally wilt before one's eyes, although in the average case the emaciation is progressive. The increase of catabolic wastes thus adds further to the factors already goading the thyroid to inordinate activity. When emaciation begins to appear, therefore, the **diet** must be **increased** so as to compensate for the loss, and the body must be supplied with **fats** and **carbohydrates**, milk, cream, cheese, vegetables, cereals, etc.; butcher meats should still be avoided.

As a result of this catabolic drain, moreover, the muscular elements of the entire body tend to relax, producing the prominent symptom previously emphasized, general vasodilatation. Affecting as it does all vessels, it accounts for the diarrhea, the profound muscular fatigue, the low blood-pressure, the weak cardiac systole, the exophthalmos, the headache, the cutaneous heat, flushes, pruritus and hyperidrosis. At this point a special line of treatment to control the functions of the thyroid directly becomes necessary.

Inhibition of Thyroid Activity.—The most helpful remedies in this connection are the vasoconstrictors. **Ergotin,** first used by Huchard, and the **salicylates,** recommended by Babinski, are the best of these. Forchheimer's use of ergotin with **quinin hydrobromid** was fully warranted, the quinin adding not only its vasoconstrictor effects to those of ergotin, but tending also, by stimulating phagocytosis, to aid the defensive functions; hence its good effects in some cases. The writer prefers a combination including sodium salicylate, which also stimulates hepatic antitoxis. The formula used is as follows:

℞

Ergotinæ...................... ʒ ss (2 grams)
Sodii salicylatis
Quininæ hydrobromidi.........āā ʒ ii ss (10 grams)

M. et ft. capsulas xxx
Sig.: Two capsules three times daily one hour after a meal.

Owing to the bromin-ion in the quinin hydrobromid, the tinnitus aurium is practically prevented. In some instances, however, it persists; or again it is at times advisable to interrupt the use of ergotin. Under these conditions its vasoconstrictor effect, particularly if there is headache, may be sustained by giving:

℞

Acetphenetidini
Caffeinæ citratis...........āā grains xx (1.3 grams)
Sodii bicarbonatis.......... grains x (0.65 gram)

M. et ft. capsulas x
Sig.: Two capsules four times a day at equal intervals.

The caffein acts also by producing increased vasoconstriction. Other agents which tend to affect the vessels similarly are: **aspirin, pituitary gland, adrenalin, scopolamin** and **spartein.**

In many cases, it is necessary, furthermore, to directly inhibit the hypersensitiveness of the centers which govern the secretory function of the organ, *i.e.,* the sympathetic center. We have seen that the bromin-ion in the quinin hydrobromid fulfills this rôle; but in most instances the quantity in the latter salt is inadequate to meet the needs of the process satisfactorily. **Bromid of sodium,** 15 grains (0.972 gram) in a glassful of water, on retiring, is usually effective for this purpose, besides favoring sleep by quieting the heart. In fact, insomnia is occasionally a troublesome symptom in these cases; if the heart is in good condition, even though tachycardia prevails, **chloral hydrate,** 5 grains (0.324 gram) should be added to each dose of bromid. **Veronal** should be **avoided,** owing to its paralyzing influence upon the precapillary vessels. **Scopolamin,** in 1/100 grain (0.00065 gram) doses, has been recommended, but its depressing effects are to be borne in mind, particularly when the heart is at all dilated.

Some of the cases show clear landmarks of hysteria. In all such the following formula will be found to be advantageous:

℞

Arsenici trioxidi...............grain i (0.065 gram)
Extracti sumbul
Extracti valerianæ
Extracti asafœtidæ............ āā ʒ ii (7.80 grams)

M. To be divided into sixty (60) chocolate-covered pills.
Sig.: One pill night and morning.

The functions of the thyroid, as shown by Bedart and Mabile, may also be depressed by **arsenical preparations. Fowler's solution,** in a dosage beginning with 3 minims (0.18 c.c.) in a glassful of water after meals, and gradually increasing until 5 minims (0.3 c.c.) are taken, is at times very efficient, but the latter dose should cause peripheral vasodilatation. Its action in this connection is due to the fact that, as stated by Cushny, "arsenic lessens oxidation of the tissues." Lauder Brunton found that it interfered with normal metabolism; this finding was further sustained by the observation of Chittenden and Cummins, that it reduced the excretion of carbon dioxid. Arsenic thus interferes with one of the most harmful features of the morbid process. **Atoxyl, sodium cacodylate, arsenobenzol** and other arsenical preparations have been tried, but appear to have no special advantage. When given in pills, the trioxid should be used in 1/60 grain (0.001 gram) doses.

Various **sera** have been advocated by some and found ineffective by others. They include that of Rogers and Beebe, prepared by injecting a nucleoproteid and a thyreoglobulin into rabbits; another, obtained from thyroidectomized goats, and supposed to counteract the toxic action of the patient's excessive thyroid product; antithyroidin, a German product; thyroidectin, a powder precipitated from the blood of the thyroidectomized sheep; and rodagen, a mixture of dried milk from thyroidectomized goats and sugar of milk.

Finally, the internal remedies include those which tend to restore to the nerve-cells their functional constituents, through the destructive action of the thyroid hormone upon their fatty bodies. The phosphorus-laden nucleins which **thymus gland** contains fill this need admirably; 5 grains (0.324 gram) of the desiccated gland may be given three times daily after meals; **sweet-bread** cooked in various ways, in order to avoid sameness and to appeal to the patient's appetite, may also be given every day. Besides supplying nucleins, this food contains fat which is easily assimilated—the nervous elements probably receiving their share. It seems also to protect the nervous system by compensating for the fats catabolized by the thyroid hormone. **Lecithin** is another useful agent for the rebuilding of the nerve-cell. The most satisfactory preparation is the French granular lecithin of Clin-Fougera, a spoonful of which (the spoon is furnished with each package) may be given three times a day.

Also helpful in the same direction is the official **syrup of calcium lactophosphate,** particularly when the tremor is marked, in 2 dram (7.8 gram) doses after meals. The calcium also increases the tone of the cardiac and vascular muscles. Where there is reason to believe that the primary toxin is of intestinal origin, **sodium phosphate,** employed, as we have seen, as an aperient in 1 dram (3.90 gram) doses, morning and evening, in a glassful of warm water, also contributes to the upbuilding of the impaired nervous system by means of the salt absorbed. The **glycerophosphates** are also useful for this purpose.

Auxiliary Measures.—The agents enumerated afford an ample armamentarium medicum for the successful treatment of practically any case, when that case is regarded as a unit, and the measures are adjusted to its special needs. When, however, remedies fail, we must resort to the aid of auxiliary measures.

The writer has found *x*-ray treatment of considerable value in preventing the recurrence of hyperthyroidism, after its successful medical treatment. The *x*-rays are also particularly useful in cases in which the thymus is enlarged, a fact which should be ascertained by means of a preliminary roentgenogram. An increase in weight and a decrease in pulse-rate indicate improvement, due to reduction of the excessive activity of the glands. Too prolonged a use of this treatment, however, may result in hypothyroidism. The cardinal objective signs are seldom removed. Some have held that irradiation complicates surgical procedures, by promoting the formation of adhesions.

Radium, used in conjunction with the general treatment, is said to have given better results. Aikins,[70] for instance, states that he obtained clinical recovery in 50 per cent. of his cases by the use of this method.

The **hot water injections** introduced by M. F. Porter[71] aim to destroy areas of thyroid tissues by scalding them, thus diminishing the secretory power of the gland and its volume, the beneficial effect consisting in the fibrous tissue formed. The quantity injected at one time varies from 40 minims (2.5 c.c.) to 10 drams (37.25 c.c.). Due care must be taken to avoid the large superficial veins and to inject inside the capsule. The skin, after being cleansed, is anesthetized by Schleich's method. A large, glass, graduated syringe, with a long, rather fine needle, is boiled in the water used for the injection. When more than one injection is given at one sitting, the syringe proper, handled with long forceps, is reboiled each time, in order that the water may always be as near boiling as possible. "With a long needle different areas may be injected through the same skin puncture by partly withdrawing the needle. In this way both the right and left lobes and the isthmus may be injected through one skin puncture, made in the center of the neck." No untoward phenomena were observed by Porter other than a fleeting headache. The method caused one death in a case at the Mayo Clinic with a very high degree of toxis. Other observers have reported good results.

Quinin and **urea injections** are used by L. F. Watson[72] to relieve hyperthyroidism. They are preceded by injections of sterile salt solution and sterile water, in order to raise the patient's threshold to stimuli. The strength of the quinin and urea solution depends upon the type of the goiter and the character of the symptoms. Only one injection is given at a treatment, which is repeated at intervals of from two to six days. From ten to twenty injections are usually required to produce marked improvement. The first injections are usually given at the upper pole; when the thrill over the superior thyroid has diminished, the injection with the lower pole is made, and, finally, that into the central portion. A few minims of the concentrated quinin and urea solution are given at a treatment. The toxic cases should be watched carefully, and at the first sign of an acute exacerbation of hyperthyroidism treatment should be stopped, a hypodermic of **morphin, atropin,** and **digitalin** should be given, and **ice-bags** applied over the thyroid and heart.

Surgical Measures.—Even in the hands of good average surgeons the ultimate recoveries, persisting several years, hardly exceed 30 per cent. (*See under* Prognosis *below.*) The reason for this appears to be that, as in the case of the physician, the surgeon overlooks the primary cause of the disease—intoxication—which goads the thyroid apparatus to excessive activity. After partial thyroidectomy there is continued excitation of the portion of the organ left *in situ,* and in the majority of cases only "improvement," a condition far removed from "cure," judging from cases which the writer has had to treat. He has found that if too much glandular tissue is removed, a condition worse than myxedema is the remote result. If the causative infection or auto-intoxication is first carefully removed and treatment on the lines advocated in the foregoing pages—in which random medication has no place—is instituted, the great majority of cases will not require operation. If, however, owing to the pathological sensitiveness of the gland due to prolonged excitation, operation becomes necessary—either **ligation** of the main thyroid **arteries** or **partial thyroidectomy**—the surgeon will also obtain lasting recovery in practically all uncomplicated cases, provided the primary toxic factor has actually been found and eliminated.

Pathology.—Summarizing the foregoing pages we are brought to realize that the thyroid gland bears the brunt of two toxic factors: (1) the primary toxin derived from a focal infection or, in cases due to emotional stress, the toxic wastes of neural origin; (2) the excessive catabolic wastes derived from all tissues, the formation of which the thyroid itself provokes, as a result of the excess of hormone which it secretes under the influence of the primary toxin or poison. The histological lesions in the organ should, therefore, be those of excessive functional activity with, as is the case with the heart when it is overworked, signs of hypertrophy.

This is precisely what modern research has found to be the case. As H. S. Plummer, of the Mayo Clinic,[73] found after a study of the basal metabolic rates of about 2,000 cases, the thyroid gland in exophthalmic goiter did quantitatively one-half again as much work as did the normal thyroid. He states, furthermore, that a certain metabolic rate would continue without the thyroid, but "at a very low ebb." This indicates the preponderating rôle which the thyroid gland plays in general metabolism. Referring to a comparative histological study of 5,000 thyroids removed from patients with non-symptomatic or non-toxic goiters, and an equal number of toxic goiters taken from patients suffering from hyperthyroidism, or Graves' disease, Louis B. Wilson[74] writes: "While we are as yet unable to make positive statements concerning the physiologic basis of these two types it will probably be found that the non-toxic non-exophthalmic type is due to over-function of the tissue most frequently [manifested] in a benign new growth, while one group of symptoms of toxic exophthalmic goiter are due to over-function of the parenchyma of the normal gland, which has been excited to hypertrophy and hyperplasia by direct stimulation from its nerve supply." The histological examination of the thousands of pathological specimens referred to clearly indicated an increase in functional activity. Kocher,[75] in a report based upon the study of over 700 removed glands, states that he "always found histological changes in the thyroid, likewise a hypersecretion, and in this an increased iodin content."

The histological changes are typical. The alveoli containing the colloid, which was found recently by Kendall not to contain the secretory principle of the gland—contrary to prevailing teachings—are enlarged and irregular, their epithelial elements increased and converted into cylindrical columnar superimposed irregular layers. Attempts at forming new alveoli are suggested by accumulations of cells, which have been compared by Wilson to those observed in malignant adenoma. These changes are not always observed throughout, but, as observed by Kocher, may be circumscribed. Gradually as these changes, due to overactivity, proceed, connective tissue areas gradually form, and increasingly encroach upon the secretory elements. There comes a time when, through sufficient reduction of the latter, normal conditions are apparently restored, the hyperactivity of the gland being reduced to normal activity. This coincides with a period during which comparative comfort is experienced by the patient. Unfortunately, the connective tissue invasion continues, and eventually the case becomes transformed from one of hyperthyroidism into one of hypothyroidism with symptoms of myxedema, first merged with some of Graves' disease. After a time, the degenerative process in the gland persisting, typical myxedema sets in with a degree of severity seldom witnessed in primary cases of the disease. The severity is readily accounted for when it is realized that the ravages of the disease are exerted upon an organism already injured by excessive, and therefore destructive, metabolism.

A complicating factor, and one which probably accounts for the stubbornness with which some symptoms persist even after partial thyroidectomy, is the presence in the enlarged gland of circumscribed new growths, which have been grouped as "thyroid adenomata." According to Goetsch,[76] these circumscribed growths may show every conceivable type of histological picture. Although able to provoke hyperthyroidism by irritating the neighboring secretory elements, they also possess the property of taking up iodin, and metabolizing it into the active hormone. They develop from interstitial rests occurring probably in all normal glands and, under the influence of excitement, pregnancy, a toxemia, etc., grow either rapidly or slowly, and, as is often the case, undergo degeneration.

Prognosis.—The statistics published by various authors concerning the proportion of cases cured by medical and surgical treatment do not afford a reliable basis for an estimate of the number which were actually cured, unless several years are allowed to elapse after the patient is discharged. The average physician, when considering the results of operative treatment, is misled by the published statements that Kocher observed a mortality of 1.53 per cent., while the Mayos reduced theirs to less than 1 per cent. This refers only to the *operative* mortality. But the ultimate results, even those obtained by such experts, tell a different story. Judd and Pemberton,[77] of the Mayo Clinic, for instance, give 45 per cent. as the proportion cured eight years after operation. Starck,[78] reviewing the final results obtained by several prominent German surgeons, places their ultimate cures at approximately 30 per cent. While this country contains many surgeons of the first order, can we conscientiously admit that they all possess the skill of Kocher or of the Mayos in thyroid surgery—admittedly precarious in many of its phases? Again, we must concede that all surgeons cannot be graded as first-class operators, and that the operative mortality grows apace with deficiency of operative skill. To place the mortality rate at 6 per cent., and the ultimate result, after four years, for instance, at 18 per cent., is to over-rate the ability of surgeons other than those of the first order.

Medical treatment, even on the empirical lines given in text-books, affords a better showing. While Syllaba[79] does not have to impose upon his patient the test of "operative mortality," his percentage, based upon 51 cases of fifteen years' standing, gave over 33 per cent. as the average rate of recovery reported by physicians.

When physicians have learned to depend mainly upon the removal of the primary factor of the disease: the source of the toxin or toxic factor which starts the thyroid on its thyrotoxic rampage, they will greatly increase the proportion of permanent cures. A prominent author who represents the attitude of most writers, states: "So long as there is no specific medicine for Graves' disease, the little which can be done is based purely on symptomatic treatment." Such measures are sure to fail in any case in which a toxic focus of any kind continues to perpetuate the excessive functional activity of the thyroid. Or, the symptomatic treatment may only serve to mitigate the symptoms until the primary source of the toxemia disappears under the influence of Nature's efforts. This is the probable explanation of those cures—hardly one-third of those seen—which are obtained by the symptomatic method.

The search for a specific will continue to be as unsuccessful as it has always been, because of the multiplicity of toxic factors which may initiate the disease. Each case has its own specific treatment, *i.e.*, that of the causative disorder. This was well exemplified by one of the writer's cases, which had reached the stage of mental aberration. Removal of eleven badly abscessed teeth, and absolute rest, brought about complete recovery, and the patient has not shown a single sign of her disease during the five years which have elapsed since her discharge. The same results have followed in cases of intestinal stasis, and also in the case of patients suffering from tonsillar abscesses, nasal suppurative disorders, etc. It is, therefore, vain to speak of a specific in such circumstances, even though the militant factor is a ubiquitous one: excessive outpouring of thyroid secretion, with systemic vasodilatation and destructive catabolism as the ultimate result.

Briefly, very few diseases offer a prognosis as favorable as that of hyperthyroidism or Graves' disease, provided the pathogenic factor can be brought to light and removed, and the damage to the organism repaired by measures carefully adjusted to each lesion which is discovered.

CRETINISM (INFANTILE MYXEDEMA)

Definition.—Cretinism is a chronic disorder of infancy, childhood and adolescence due to deficient functional activity of the thyroid gland while the body, including the cerebrospinal system, is undergoing development.

Etiology and Pathogenesis.—These are intimately blended with the causes and pathogenesis of goiter (*q. v.*); cretins and goitrous individuals, insofar as the endemic form of these diseases go, are found in the same district. Moreover, the goitrous individual and the cretin are obviously subject to similar etiological factors, the cretin being often afflicted with a goiter.

In respect to the relationship between goiter and cretinism, McCarrison,[80] in a study of this subject in white rats, found that a small percentage of the offspring of goitrous parents are born cretins, and that nearly two-thirds are born with congenital goiters. He considers that these two conditions, cretinism and congenital goiter, are due to the action of *toxic substances* derived from the intestines of the goitrous mother on the thyroparathyroid mechanism. Cretinism represents, in his opinion, the maximum, although comparatively rare, effects of these toxins, and congenital goiter their minimum and comparatively common effect. Between these extremes may occur, with or without associated swelling of the gland, all degrees of thyroid involvement.

This corresponds to a material degree with clinical experience as to foci of *endemic* goiter and cretinism. We occasionally see cretins born of goitrous parents, but the latter bear a large proportion of children whose thyroid gland is deficient, although not deficient to the extent of evoking cretinism, whether or not the gland is enlarged, or even atrophic. Such a gland may function with sufficient activity to carry out its necessary part in the metabolism and defense against intermediate (toxic) wastes which a perfectly normal vital process requires. As soon, however, as any extra work is imposed upon it, through the presence of an excess of endogenous or exogenous poisons, including toxins, it becomes pathological, after an effort at compensation through over-activity, then virtually functionless, thus provoking cretinism. These toxins may originate from microörganisms in the intestinal canal, ingested with contaminated water, or may be derived from any other source, such as a debilitation of the thyroid.

In *sporadic* cretinism, which may occur anywhere and in regions in which endemic foci may not exist, and in healthy families, some *lesion of the thyroid*, such as hemorrhagic foci, or perhaps necrotic areas due to autolysis, probably always underlies the morbid process. Either of these lesions may be brought about in the course of one of the many *diseases of childhood*, or other general infections. The efficiency of the gland is reduced in proportion to the amount of tissue sacrificed by the morbid process, or the local degenerated tissues following that process. Hence the fact that in such cases the parents will usually declare that the child was perfectly normal until it had measles, scarlet fever, pertussis, etc., or perhaps typhoid fever, pneumonia, etc., after which it failed to develop and ultimately showed all the signs of true cretinism.

Symptomatology.—The disorder may be manifest at birth, that is to say, it may be congenital. In a case observed by Abels, for instance, the infant presented the following picture a few hours after birth:

The skin was bluish-red, and cool, without any apparent cyanosis of the mucous membranes; the mouth was wide open, with the tongue protruding; the lips were thick; there was almost constant wrinkling of the fleshy forehead, and a bag-like protrusion of the upper lids; the cheeks were broad and somewhat hanging; an abundance of long, soft hair grew down over the forehead and cheeks; the neck was strikingly short, with a slight arching of the supraclavicular region; the fontanel was normal in size, and had hard borders; the bridge of the nose was flat; the tibiæ was markedly bowed. Within the next few days the diagnosis of congenital myxedema was confirmed by the continuous pronounced hypothermia of from 34.5° to 35° C. (94.1° to 95° F.). The weight at birth was 3,090 grams (6 1/5 pounds). Protracted bradycardia of about 104, bulging of the abdomen, moderate constipation and general sluggishness were noted. The infant died at the age of five weeks of bronchopneumonia. Autopsy revealed complete absence of the thyroid, small cysts in the upper pair of parathyroid bodies, a characteristic tumor at the root of the tongue, and an abnormally small thymus. The mother of the infant, her sisters, and the infant's father, showed evidence of goiter.

As a rule, however, cretinism is seldom recognized until the fourth or fifth month, unless the tongue is large and protruding and the tendency to hypothermia is noticed. The infant fails to grow normally, and does not show evidences of developing mentality. The tongue seems to be unusually large and thick, sufficiently so in some cases to prevent approximation of the lips and to interfere with respiration. The infant is unusually quiet and apathetic and seldom cries. It fails to show a normal interest in its surroundings or even in its parents. Its face is unusually expressionless, and no pleasure is manifested at things or events which usually please or attract an infant. It exhibits no desire, except perhaps for food or beverages; appetite is usually manifested by grunts or inarticulate sounds.

The skin may be soft in the milder cases, but as a rule it is dry, scaly, and may even be furfuraceous in the more marked instances. As a rule, it fails to pit on pressure and may be swollen, although firm under pressure. Although the hair may be thin, in rare cases, it is usually thick and coarse. It may show no tendency to grow in the axillæ or on the pubis; the eyebrows and lashes may be sparse or even absent.

Children thus affected have a wizened appearance, suggesting that of very aged people, and may greatly resemble one another. The forehead is low and furrowed, and the expression lifeless and stupid. The nose is squatty and broad (saddle-nose), the eyelids thick and perhaps puffy, giving the eyes the slit-like appearance of some Chinese. The few teeth are irregular and more or less decayed; the second dentition may not appear at all, or if it does, it is delayed and the teeth are carious—rendering the breath very fetid. Saliva drops from the mouth to such a degree in some cases as to keep the chin constantly wet. The lips usually overhang, and are thick and often cyanotic. The swollen condition of the tongue, gums and oral mucosa renders it necessary to feed the child fluid or semifluid foods with a spoon. As the mucous membrane of the respiratory tract is also edematous, the voice is hoarse or raucous. The skin is pale, or more exactly, waxy, and dirty in color, with occasionally some suffusion of the cheeks. The head is always overlarge, is usually misshapen, flattened anteroposteriorly, and enlarged in the occipital region; the cheek bones and palatal arches are high. The fontanels remain open abnormally long, sometimes until puberty.

When the child is young the muscles of the neck may be unable to support the head, and the latter falls forward. In some instances, it may even rest upon the chest. The form of the neck is characteristic in that it broadens, in most cases, as it approaches the shoulders, a fact due to the presence of pads of fat in the suprascapular region which more or less enlarge the lower part of the neck, assuming in marked cases the appearance of a thick collar. The shape of the neck is further altered by the fact that the thyroid gland itself can not be palpated, owing to its atrophied state, or that it may be goitrous, particularly in the endemic form. In occasional cases, however, the glands appear to be clinically normal.

The body and extremities are also characteristic in appearance. The abdomen is usually very large, the child being decidedly pot-bellied. This is accentuated by the fact that the back is deeply arched anteriorly, owing to the weakness of its musculature. Umbilical hernia is usually present, although rarely pronounced. The arms, hands, legs and feet are short, stunted and pudgy, the thickened skin forming folds or irregular masses. The fingers and toes are in a similar state, and tend to stand apart, thus rendering the motions clumsy. The nails are dry, brittle and short, and their surface striated or streaked with areas of white, denoting localized detachment from their underlying bed. Sensation being impaired, the patients are not as sensitive to pain as is the average child, and seldom show evidences of suffering.

The genital organs fail to develop, and retain the infantile type, in both males and females. In some instances there is a certain degree of development, but as a rule the sexual appetite is blunted. The small number of individuals in whom it develops after puberty are fortunately sterile.

Short stature is characteristic of cretinism, the growth of the skeleton being greatly impaired. Cretins are practically all dwarfs and seldom attain four feet in height even as adults. The arms and legs of cretins are stunted. They are often bow-legged. The long bones of the legs are relatively thick, but they are deformed as in rickets. The vertebræ, the ribs and the pelvis are also affected, and the gait of a cretin is often irregular and awkward. The skull is thick, and prognathism is common.

The degree of idiocy varies considerably with each case. Combe has divided cretins into three classes which approximately represent the stages met in practice: The *first class* includes individuals whom Roesch has aptly termed "human plants"; in these cases the condition is usually congenital, the thyroid is virtually inactive, and the life of the subject is purely vegetative. These individuals fail to grow, and eat only when fed. They are absolutely idiotic and inert; they have practically no sense of taste, smell or touch. As a rule, they die early, but some have even exceeded the "four score and ten" span. The *second class* includes the "semicretins" or "micretins." Roesch has styled these "human animals," because the average animal can do all they can. It is the opinion of the writer that these cases are usually the result of the impairment, in infancy, of the functional activity of the thyroid by some infectious disease. Patients of this type retain such development, physical and mental, as they have acquired at the time the morbid process begins. They may manifest pleasure, interest, discontent, greed for food, etc., and they may be taught to be clean, to carry objects, etc. The *third class* is relatively large and includes subjects in a "cretinoid state" as described by Combe. Many of the dullards of our schools belong to this type. In the opinion of the writer this condition is also traceable to postnatal lesions of the thyroid. There is merely a heaviness of mind, and more or less difficulty in comprehension, characteristic neither of an imbecile nor of an idiot, but merely distinguishing the child as backward or "cretinoid."

The internal organs appear to functionate normally. This is not true of the genital organs, which, we have seen, are small and atrophied; however, girls may menstruate profusely. Thus the heart, lungs, liver, spleen, stomach and kidneys do not appear to be the seat of disorder more frequently than is the case in normal subjects. The intestinal canal is torpid, however, and obstinate constipation is the rule.

An important feature of these cases is their sensitiveness to the action of toxics. Many congenital cretins of the "human plant" type die very early in the course of an epileptic convulsion due to toxic waste products; the blood of cretins, we have seen, is exceedingly toxic. All cretins are extremely sensitive to the action of alcohol. They greatly dislike meat, which, as we have seen, is toxic to thyroidectomized animals.

On the whole, cretinism is found to be due essentially to deficient or slowed metabolic activity resulting from absence, atrophy or hypoplasia of the thyroid gland. This is in keeping with the physiological data submitted above. The low internal (and often external) temperature, the great sensitiveness to cold, and the low excretion of urea, point to deficient oxidation. The myxedematous swellings in fat pads, the thickened tongue and lips, are probably due to the vascular atony and dilatation, the result in turn of the universal myasthenia and due to the same underlying cause, *i.e.*, slowed or defective metabolism. The latter accounts also for the stunted growth, but here another feature reviewed is recalled, *viz.*, defective calcium metabolism, a function, we have seen, with which the parathyroids are concerned. Finally, the vulnerability of cretins to disease and to poisons indicates impairment of the defensive functions in which, as we have seen, the thyroparathyroid apparatus takes part.

Diagnosis.—The cretinic facies are so characteristic—the saddle-nose, more or less swollen lids, tongue and lips, the harsh skin and coarse hair, in conjunction with the stunted growth—that marked cretinism may at once be recognized. The cretinoid type is more difficult to identify, but this question will be taken up again under the heading Hypothyroidia. In the present connection only the well-marked types of cretinism will be considered—those readily recognized clinically, as just stated. The disorders with which these types may be confused are described below.

In *mongolism*, the slanting eyes, the normal hair and nails, the absence of myxedema, the greater interest in surroundings, the greater effort to speak and play, the affectionate and sociable nature of the child and the far less repulsive appearance, render identification easy in most cases. In several cases seen by the writer, however, various cretinoid symptoms were present. In case of doubt treatment with thyroid gland will soon settle the diagnosis. The cretin will show rapid improvement, while the mongolian idiot will show but little, if any.

In *amaurotic family idiocy,* infants between the fifth and tenth month fail to develop physically and mentally. But here, besides the progressive myasthenia which finally renders the little patient unable to hold up its head, to sit or to grasp, and also the marked pallor, there is gradual loss of vision; the infant fails increasingly to notice its mother or nurse and also ignores objects which before attracted its attention. None of the thyroid stigmata may be said to be present.

In *dystrophia adiposogenitalis* or Fröhlich's disease, various cretinoid stigmata may appear, such as fat-pads, harsh skin, arrested development of the genital organs, absence of hair about the pubis and axillæ, etc. If the disorder has begun very early in life growth may be stunted, but otherwise the patients are taller than cretins. In fact, in 2 of the writer's cases, the height was above normal, probably owing to overactivity of the pituitary body early in the development of the case. The typical moon-face totally differs from the cretinic facies, while the feminine type of the body, and the greater mental development, serve to identify these cases.

In *achondroplasia* (fetal rickets) the conformation of the body and the stunted growth may suggest cretinism, but the only real deformity is found in the bones of the legs and arms, which are relatively short. There is marked malformation of the cartilages, the articulations usually being very large. There is no edema, the genital apparatus, hair supply and intelligence are normal, as are also the temperature, pulse and blood-pressure, since there is no thyroid insufficiency.

Ordinary rickets, microsomia, adiposis dolorosa, hydrocephalus and *infantilism* have also been thought to resemble cretinism; but, in reality, with the slightest care one may avoid all confusion, so typical is the cretinic facies.

Treatment.—Prior to the introduction of thyroid gland therapy nothing seriously modified the morbid process. **Thyroid gland** virtually acts as a specific in both types of cretinism, provided its use is begun early, *i.e.,* soon after the development of the disease, and early in life. In such cases the results are striking; sometimes the child grows over an inch per month until the normal stature for the corresponding age has been attained. As regards mental development, the results, while remarkable, are not as satisfactory, a high grade of intelligence being seldom attained. Where an interval of years has elapsed between the onset of cretinism and the beginning of treatment, the regained intelligence does not, as a rule, by any means equal that of the normal child.

Careful adjustment of dosage is necessary. Large doses not only entail danger of sudden heart-failure, but may also lead to softening of the bones owing to an unduly rapid growth. This may be guarded against, if the bones begin to yield, by the application of suitable braces.

At times toxic symptoms may develop in a sudden, unexpected manner, the drug being in a sense cumulative in its action. Such untoward effects are more likely to appear when the glandular preparation used is old. An infant can, as a rule, be given ½ grain (0.0324 gram) of dried thyroid once daily, a child of two years, twice daily, and older children, three times daily; or the latter may be given 1 grain (0.065 gram) twice daily. Murray recommends that, as a precautionary measure, the child should be kept recumbent after the last dose, which is given late in the day. When the normal body temperature has been reached, under the influence of the treatment, 1 grain (0.065 gram) of dried thyroid on retiring will, as a rule, be sufficient to prevent recurrence. Danger signals necessitating a reduction in dosage include: a rapid pulse, dizziness, pains in the back and extremities, general weakness, and a syncopal tendency, or, ultimately, nausea and vomiting, a pronounced rise of temperature, and collapse.

In cretins who have reached adult age before treatment is begun, improvement is slight, or may be *nil*. Again, in sporadic cases, the improvement is more marked than in the endemic, irreparable injury to the gland having often been produced in the latter type before treatment, while in the former the earliest, most important, stages of growth may have been passed before the onset of the disease.

In order to forestall any tendency to softening of the bones, the administration of **syrup of lactophosphate of lime** in teaspoonful doses may prove a useful adjuvant to thyroid treatment. Dried **thymus gland**, 5 grains (0.324 gram), thrice daily, is also of advantage.

Thyroid grafting, to obviate the necessity of thyroid medication throughout life, has been rather widely experimented with, but the results, on the whole, have been disappointing. According to Cristiani,[81] the grafts must be of normal human thyroid tissue, and must be introduced only into very vascular subcutaneous tissue, in small but multiple masses. However, Charrin and Cristiani[82] obtained good results with sheep's thyroid as well. In a series of cases the latter observer[83] noted distinct improvement in 60 per cent., remarkable results in 34 per cent., and no improvement in 6 per cent. of the instances. Kummer[84] has reported a successful autograft of normal segments of the thyroid under the skin over the right acromion in a woman with a large goiter. Both lobes of the goiter had been almost completely removed.

Charles Goodman[85] concluded, from experimental work on dogs, that as yet no means were available for indefinitely prolonging the life of an entire organ transplanted from one animal to another. He agrees with Carrel, Lexer, and others, however, that autotransplantation is practicable. In his experiments the arterial supply of the transplant was provided for by the suture of an attached segment of carotid into the carotid of the host, and the venous supply by end-to-end suture of the thyroid vein with the central end of the external jugular vein of the opposite side. In autotransplantation, the author thus succeeded in two consecutive instances in retraining the thyroid gland in its normal state microscopically. Among the homotransplantations there were a few instances in which the parathyroid remained normal while the thyroid showed evidences of hemolysis.

Kocher,[86] while recognizing that thyroid transplantation acted even more effectually and promptly than thyroid medication in myxedematous states, concluded that a single transplantation was insufficient, and asserted that a possible method of obtaining a permanently active transplant would be to decrease the immunity of the recipient, such immunity tending to hasten the destruction of the transplanted tissue.

Pathology.—In the endemic type, the gland usually shows a more or less marked proliferation of connective tissue, and deficiency amounting to virtual obliteration in advanced cases of the glandular tissue with thickening of the vascular adventitia. In the sporadic form, fibrous or degenerative areas may also be found, where hemorrhagic or necrotic foci occurred at the time of the causative infection, but when the lesions have been punctiform, the pathological findings do not differ appreciably from those in the endemic form.

MYXEDEMA OR PROGRESSIVE HYPOTHYROIDISM

Definition.—Myxedema is a chronic progressive disease of adults due to deficient functional activity of the thyroid gland, and characterized by lowered oxidation and catabolism, the main symptoms of which are hypothermia, myxedematous infiltration of the cutaneous tissues, increase in weight, dryness of the skin, asthenia and mental torpor.

Etiology and Pathogenesis.—Myxedema, encountered in practice with comparative rarity, is to the adult what cretinism is to the child, but it differs from the latter condition in that after the completion of development and growth, mental and physical, its effects are purely those of deficient metabolism. We have seen that the thyroid plays an important rôle in metabolism, while vulnerability to disease exemplifies anew the participation of the gland in the defensive processes.

Myxedema is often traceable to *heredity,* many families showing several instances of the disease. It occurs to a much greater extent in *women* than in men, the ratio being about six to one, a fact accounted for by the frequency with which the disease is due to frequent childbearing, the menopause, worry, emotional stress, etc. This is particularly true in *predisposed* subjects, the predisposing antecedents being goiter, tuberculosis, neuroses, alcoholism, and syphilis. The results of *local lesions* in the thyroid, hemorrhagic or inflammatory neoplasms, fungi, entozoa, and tumors capable of materially reducing the secretory area of the gland, may also cause the disease. While it may develop at any time after puberty, it is most frequently encountered between the *thirteenth* and *sixtieth year.*

The gland is usually found to be the seat of fibrous tissue areas formed at the expense of the true glandular tissue. This is accounted for by the fact that the causal factors include local *inflammatory processes* in the course of acute articular rheumatism, erysipelas, syphilis, actinomycosis, cancer, acute thyroiditis, local injuries, etc. Where repeated child-bearing, shock, menopause and other non-bacterial factors prevail as causative factors, local lesions are seldom found, a fact which points to secretory exhaustion of the gland as the source of its failure to carry on its functions.

Symptomatology.—The predominating feature of these cases being deficient oxidation and metabolism, the patients suffer almost continuously from cold, except in warm weather. The temperature is always below normal and, the circulation as well as the processes of oxygenation being impaired, the least exposure to cold induces cyanosis of the peripheral tissues. Another striking feature in these cases is the tissue infiltration, or edema, which gives the disease its name "myxedema." It differs from true edema in that the tissue is firm and elastic, and does not pit on pressure. The tissues of the face being likewise infiltrated, the features are mask-like, and devoid of expression or mobility, while the eyes are more or less closed by the thickened lids. The abdomen and limbs, hands and feet are also thickened by the myxedematous infiltration. This accounts for the increase in weight, sometimes very marked, noted in the case of these patients. All the mucous membranes similarly become pale and tumefied, the condition of the teeth and gums proceeds from bad to worse, and the attending stomatitis and salivation result in dribbling from the corners of the mouth. Enunciation is imperfect, and the voice coarse, nasal, and low-pitched.

The skin is dry, rough and scaly in well-marked cases, much as it is in cretinism, the nails being brittle and thin, sometimes ridged, and atrophied. Patches of pigmentation, varying from yellowish brown to actual bronzing, and suggesting participation of the adrenals in the functional torpor, are sometimes observed. The hair loses its luster, becomes coarse and brittle, and finally falls out. Constipation alternates with diarrhea, and there is a profound distaste for meat.

The patients show a marked tendency to somnolence, apathy, amnesia and irritability and, in some instances, to mental disorders. Exhaustion upon slight exertion is the rule. Sensation is impaired and the finer movements imperfectly performed. Headache and pains in the muscles and joints are common. The special senses are obtunded or perverted, and hemorrhages, apparently due to poverty of the blood in fibrin ferment, are common. Urea excretion is diminished.

A distinct reduction in the size of the thyroid gland, the seat of atrophic change, occurs in the vast majority of cases of myxedema. At times, however, the gland is actually enlarged at first, and then gradually atrophies irregularly.

Death eventually occurs from exhaustion or from some intercurrent infection. As a rule the condition lasts from six to twenty years; but occasionally, especially in young adults, it may run its course in six months. An acute type of myxedema, with death within a few days, has also been observed.

Treatment.—Striking results are obtainable in this condition by **thyroid feeding.** The patient is soon restored to his normal condition by this method. One grain (0.065 gram) of dried thyroid three times a day is sufficient at first, but this dose may later be gradually increased to 2 grains (0.13 gram) or more. Restoration of the body temperature to normal is a useful guide as to the amount actually required. If the temperature rises above normal the dose should be reduced. The pulse-rate should also be watched, an increase of 15 beats per minute indicating the necessity for a reduction of the dose. Excretion is to be avoided during the treatment, especially at first, for fear syncope might suddenly supervene.

To maintain the improvement, the remedy must obviously be continued throughout life, unless **thyroid grafting** is performed successfully, which is still hardly to be expected. (*See* Cretinism: Treatment, p. 259). If the heart is considerably dilated, small doses of **digitalis** or of **dried pituitary** or **suprarenal gland** will prove of material benefit.

HYPOTHYROIDISM OR LARVAL MYXEDEMA

Definition.—Hypothyroidism is a constitutional disorder due to deficient functional activity of the thyroparathyroid apparatus, and the resulting slowing of metabolism in all tissues, as manifested by slowed circulatory activity, early aging and alopecia, mental torpor—especially marked in children—susceptibility to cold, and defective resistance to infection.

Etiology and Pathogenesis.—While myxedema, reviewed in the preceding section, is rarely encountered in practice, larval, or "*fruste*" myxedema is relatively common. It is, in reality, not true myxedema, since the symptom which this term implies is absent. Yet the milder symptoms of myxedema are present, the underlying causes being the same, but far less active: *reduction of the thyroid supply* of the body at large, and therefore slowing of the functions in which this organ takes part, namely the thyroid metabolism. The word "metabolism" is used advisedly in the present connection because it denotes both anabolism and catabolism. When slight or moderate insufficiency of thyroid activity prevails, both these phases are slowed, the picture as a whole, therefore, being that of correspondingly marked slowing of both cellular interchanges—anabolism—and breaking down of wastes—catabolism. When this slowed metabolism becomes very marked in the developing child cretinism ensues; when it occurs in the adult, it causes myxedema. Both of these diseases have been reviewed in the preceding sections of this article.

Two forms must be recognized, the acquired and the hereditary. In the *acquired* form, the *diseases of childhood,* measles, scarlatina, diphtheria, mumps, etc., are probably the most prolific malefactors. This is due not only to the pathological changes occurring in the glands as a result of focal hemorrhages, which lead to the formation of fibrous areas, but also to the exhaustion of the organ during the febrile process owing to the excess of thyroid hormone produced. A child may thus grow normally, both physically and mentally, until some acute infection deprives it more or less of the *pabula vitæ* which the hormones of its various ductless glands represent. It then fails to recover, and shows the various signs of hypothyroidism. *Multiple pregnancies* tend also to promote the disorder by exhausting a thyroid which, owing to inherited deficiency or focal lesions, cannot withstand the drain imposed upon it by its defensive functions, which are repeatedly taxed to a prolonged degree. *Traumatism* or *local abscesses* may also cause the condition by reducing the secretory area of the organ.

In the *hereditary* type, the thyroid, in conjunction with other ductless glands, transmits *dyscrasias,* of which syphilis, alcoholism and gout are the main types. The foundation of the vital process—oxidation and metabolism—is thus impaired, and myasthenia and psychasthenia result. Maternal inheritance is thought to transmit hypothyroidism in most instances. The bad effects of *consanguinity in marriage* are probably due to the presence in the common ancestry of at least one of the pathogenic dyscrasiæ. Conversely, marriage to a healthy man will often cause a girl suffering from a mild hypothyroidism to be restored to health if pregnancy occurs, owing to the physiological stimulation to which the thyroid and adrenals are subjected during the development of the fetus.

Excessive *fatigue,* as noted repeatedly during the recent war, may give rise to an ephemeral form of hypothyroidism, although in predisposed cases the morbid process may show a tendency to persist unless judicious organotherapy is resorted to.

Symptomatology.—So-called rheumatic pains in the back, between the shoulders, usually cause the patient to appeal for relief. This pain is distinguished, however, by the fact that it improves on rising. Somnolence in the morning, with a subjective feeling of improvement as the day passes, chilliness, due to deficient metabolic activity, and a fondness for stimulants, are also suggestive. Other features include premature aging and grayness of the hair, a tendency to occipital alopecia, characteristically in the lateral portions of the eyebrows, dryness of the hair, a waxy hue of the facial skin, and, though rarely, puffiness of the eyelids. Dyspnea or oppression on exertion, palpitations, a tendency to cardiac dilatation, anemia, early loosening and caries of the teeth, bleeding and receding gums, due mainly to the freedom with which the *Entameba buccalis* is allowed to develop, persistent congestion of the mucosæ of the upper respiratory tract, passive enlargement of the liver and a tendency to varicose and calculous disturbances, oliguria, and flat foot, are not infrequent manifestations.

In the female sex, amenorrhea, metrorrhagia, or dysmenorrhea may be noted, and the uterus is often found to be retroflexed. Pregnancy and lactation, which we have seen excite the thyroid to increased activity, may markedly improve the condition for the time being, or, in occasional cases, permanently. On the other hand, lactation, by entailing exhausting activity on the adrenals may, at times, lead to increased pallor, a tendency to edema, and intellectual torpor. In males, impotence, spermatorrhea, and prostatic hypertrophy may be observed.

The imperfect circulation in the special sense organs, due to defective metabolism of the vascular muscularis, may lead to hallucinations of sight or to various forms of tinnitus. The mind, even in the milder cases, is apt to be more or less obtuse, and a melancholic tendency is frequent. Occasionally there is maniacal excitement, probably due to the inadequate destruction of wastes in the blood—which thus produces toxemia.

In the aged, hypothyroidia is to some extent physiological, all the ductless glands tending toward retrogression during this period—a condition which doubtless accounts for many of the disorders of senility.

Treatment.—As in true myxedema, the chief remedy is **dried thyroid gland** (*Thyroideum siccum,* U. S. P.), relief being dependent, however, upon suitable dosage. As the residual secreting power of the gland varies in different cases, careful adjustment of the dose is imperative. In adults, 1 grain (0.065 gram) of the dried gland three times a day during meals is usually sufficient at first. Later this may be gradually increased to 2 grains (0.13 gram) three times daily. More than this is seldom required, while in some cases only ½ grain (0.0324 gram), or even less, three times a day, is sufficient. Excessive dosage in any given case is likely to cause headache, pain over the kidneys and in the joints, muscles, and liver, anorexia, a rapid pulse, a rise in temperature, a tendency toward fainting, tremor, and an increase of any preexisting dyspnea, owing to excessive tissue catabolism and the resulting formation of tissue wastes. Where there is marked anemia, **dried suprarenals**, 2 grains (0.13 gram), and **Blaud's Pill-mass**, 1 grain (0.065 gram), may be advantageously combined with each dose of thyroid substance. To relieve constipation, high injections of **saline solution** two or three times a week may be required at first, after which **glycerin suppositories** may be used. For purgation by mouth, salines should be given preference. As a rule, the thyroid medication will have to be continued indefinitely, possibly in reduced dosage. Thyroid grafts, we have seen under the preceding heading, have not as yet procured permanent results.

The menorrhagia or metrorrhagia sometimes observed in these cases usually yields to thyroid treatment. The writer has found the addition thereto of dried suprarenal gland, 3 grains (0.195 gram) twice daily, a powerful aid in attaining this result.

HYPOPARATHYROIDIA OR PARATHYROID TETANY

Etiology and Pathogenesis.—Recent researches have tended to confirm the view that the parathyroid glandules enable the blood, and particularly the nervous system, to utilize its available calcium salts, by keeping them soluble. In the opinion of some writers these glandules operate in harmony with the thyroid, in the opinion of others, they operate independently. When their functions fail, due to either experimental or operative removal, tetany follows. Another function attributed to the parathyroids is that of breaking down certain toxic waste products which tend to excite the nervous system. From the writer's viewpoint, the thyroid and parathyroids form a single apparatus which, besides carrying on calcium metabolism, takes part in the defensive processes of the body at large. This is in keeping with all the facts submitted in the foregoing pages. Some of the reasons for this attitude were submitted when the physiology of the thyroid apparatus was reviewed. Experimental and clinical studies of the parathyroids alone have never been regarded by the writer as portraying their true functions, but merely that phase of the function of the thyroparathyroid apparatus in which their rôle predominates sufficiently to be identified. This accounts for the fact that tetany is the only clearly-defined expression of parathyroid insufficiency which is known. But this symptom may also occur "after slight interference with the thyroid." Kendall,[87] of the Mayo Clinic, likewise recognizes the thyroparathyroid apparatus as a functional entity, and considers the urea and ammonia output of the body to be, within certain limits, a measure of thyroparathyroid activity.

In most cases parathyroid tetany is due to *removal,* during the course of a thyroidectomy, of one or more *parathyroid glandules.* Iversen, after a study of tetany in man, concluded that two of the four parathyroids sufficed to carry on their functions. An operator, however, should conserve all the glandules if this is at all practicable. Irrespective of any surgical procedure, however, one encounters cases in which tetanic phenomena clearly suggest deficient activity of the parathyroids.

Recent studies of the subject by E. H. Pool [88] have suggested a connection between the parathyroids and morbid *sex processes* in females. Thus tetany showed a tendency to occur in menstruating, pregnant and puerperal women, and also in those who had undergone gynecological operations. While maternal tetany, lactation tetany, and the fatal tetany of the newborn of tetanic mothers, are related to parathyroid insufficiency, this is probably the result of calcium deficiency, judging from the beneficial results obtained with calcium in large doses. The effect of parathyroidectomy upon the central nervous system in animals kept alive by calcium lactate was found by Edmunds to consist in extensive chromatolysis of the brain and cord.

Symptomatology.—Tetany of parathyroid origin is characterized by typical phenomena. It differs from tetanus in that intermittent contractures of the facial muscles, back, chest and abdomen are not uniformly present, while the flexor voluntary muscles of the extremities are the seat of intermittent tonic spasms. Yet, at first, a sensation of stiffness about the mouth may occur, with twitching or trembling or tingling of the palpebral and facial muscles, followed by fibrillary contractions of the tongue and occasionally by spasm of the masseter muscles. In most instances, however, the onset is marked by a more or less severe headache with lassitude and even prostration, painful clonic twitchings or rigidity of the limbs. Clonic contractions, often symmetrical, begin at the hands; two or more fingers are flexed, with the thumb contracted on the palm, so as to form what Trousseau has termed the "obstetrician's hand" (main d'accoucheur). There are wide variations from this position, however; the hands may be claw-like, the fingers being widely separated and the terminal phalanges alone flexed. The wrists are often flexed, the forearm occasionally adducted toward the trunk. The feet are also cramped, often in the equinovarus position, the calves being frequently very painful and hard; this symptom attends all the contracted muscles in some instances.

The attack may last only a few minutes, or it may be prolonged for hours, and, in rare cases, for a couple of days. The intervals between the attacks may vary from a few hours to several days or even weeks. As a rule, however, they recur several times during the waking hours, not during sleep. There is a feeling of marked tightness about the heart and chest, owing to the contraction of the thoracic muscles; respiration may become very difficult, and cyanosis may occur. The pulse is rapid and weak and sometimes irregular, and the temperature is somewhat raised.

In *severe cases* the attacks may recur with distressing frequency, the suffering being severe. Disturbances of sensation, hyperesthesia, paresthesia, and anesthesia are frequent. Some cases present the symptoms of true tetany with opisthotonos; others may even suffer attacks of true epilepsy with frothing at the mouth, etc.

The attacks may follow the removal of the parathyroids by from one to four weeks; as a rule, however, the first signs occur about the third or fourth day after operation. In some instances, the organs are only injured during the operation; when recovery has taken place, the attacks of tetany cease. When removal has occurred the attacks may persist, and if death does not follow, the case assumes chronicity.

Mild forms of tetany sometimes result from lesions of the parathyroids, also from tuberculosis, interstitial hemorrhage, etc. Chvostek's sign—facial spasm upon tapping the facial nerve—and Hoffmann's sign —hyperesthesia upon percussion of the sensory nerves—etc., are clinical evidences of the existence of tetany. Infectious diseases may be primary causes of tetany due to injury to the parathyroids. Tetany is probably also at times a result of excessive demand upon and exhaustion of the parathyroid function or of inhibition of the activity of the glandules through the action of circulating toxic materials upon them. Whether tetany accompanying gastro-intestinal disturbances, uremia, and violent excitement or exertion, may be due to parathyroid insufficiency is not as yet definitely established.

Treatment.—Calcium lactate was found by MacCallum and Voegtlin to be helpful in tetany if given in full doses—at least 10 grains (0.65 gram) every hour or two—or by rectum in larger doses in saline solution. Absorption of calcium salts from the alimentary tract being, however, slow at best, while subcutaneous and intramuscular injections of such salts cause marked irritation, intravenous injection is by far the best procedure in emergency cases. Winternitz,[89] for example, gave 100 c.c. (3.38 fluidounces) of a 4 per cent. solution in a non-operative case of tetany, with satisfactory results. Marked benefit from calcium treatment lasts, however, only about twenty-four hours, or somewhat longer, after which the tetany symptoms begin to return, growing progressively worse thereafter.

Parathyroid extracts, given orally, appear to be of **slight value,** MacCallum having found that large quantities were necessary to produce any result. The subcutaneous use of an extract of fresh parathyroids is much more effective. Branham[90] in preparing such an extract, placed 5 fresh beef parathyroids in 1:1,000 **mercuric chlorid solution** for ten minutes, then cut them into pieces aseptically, and ground them in a mortar with 400 c.c. (13.53 fluidounces) of sterile **saline solution.** The product was finally filtered through gauze and infused under the patient's breast. Relief following the administration of parathyroid extract is only evanescent, as is the case when calcium is used.

Transplantation of parathyroid tissue suggests itself as a possible means of avoiding this. While Halsted found that autotransplantation of parathyroids is feasible in the presence of hypoparathyroidia, transplantation from other individuals has apparently never been thoroughly successful. The implant causes improvement for, perhaps, two weeks —a result sometimes sufficient to save life by tiding a patient over a critical period of parathyroid deficiency—and then becomes absorbed.

The diet is an important feature; **meats** and other **substances rich in nucleins** should be **excluded,** in order to minimize the formation of spasmogenic wastes. **Water** should be taken freely for eliminatory purposes. **Complete rest** tends to reduce the number and severity of the paroxysms.

REFERENCES

1. Kendall, E. C. The relation of the thyroid to the other ductless glands. Journal-Lancet, Dec. 1, 1917, xxxvii, 768.
2. Davis, D. J. Vaccine therapy. Jour. Amer. Med. Assn., Jan. 20, 1917, lxviii, 159.
3. Miller, J. L. The nonspecificity of vaccine therapy. Trans. Amer. Med. Assn., June 7, 1917; New York Med. Jour., June 16, 1917, cv, 1159.
4. Farrant, R. Thyroid action and reaction, with special reference to the formation of thyroid tumors. Proc. Roy. Soc. Med., Pathol. Sect., Oct. 15, 1912, vi, No. 3, p. 21.
5. Fassin, L. Influence de l'inoculation d'extraits thyroidiens sur les propriétés actives du serum. Compt. rend. de la Soc. de biol., Paris, 1907, lxii, 388.

   ——— Influence de l'ingestion de corps thyroide sur les propriétés alexiques du serum. *Ibid.,* 1907, lxii, 467.

   ——— Modifications de la teneur du serum en alexins chez lex animaux thyroidectomisés. *Ibid.,* 1907, lxii, 647.
6. Stepanoff, M. Le corps thyroide et les défenses naturelles de l'organisme Compt. rend. de la Soc. de biol., 1909, lxvi, 296.
7. Marbé, S. Les opsonines des animaux hyperthyroidés. Compt. rend. de la Soc. de biol., 1908, lxiv, 1058.
8. Palmer, C. C. The influence of partial thyroidectomy in pigs. Amer. Jour. Physiol., 1917, xlii, 572.
9. Kendall, E. C. The function of the thyroid-parathyroid apparatus. Jour. Amer. Med. Assn., 1916, lxvi, 811.
10. Marine, D. Quantitative studies on, and in vivo absorption of iodin by dogs' thyroid glands. Jour. Biol. Chem., 1915, xxii, 547.

11. **Marine and Rogoff.** How rapidly does the intact thyroid gland elaborate its specific iodin-containing hormone? Jour. Pharmacol. and Exper. Therap., 1916, ix, 1.
12. **Beebe, S. P.** Present knowledge of thyroid function. Jour. Amer. Med. Assn., Mar. 4, 1911, lvi, 658.
13. **Schöndorff, B.** Ueber den Einfluss der Schilddrüse auf dem Stoffwechsel. Archiv f. d. ges. Physiol., 1896, lxiii, 423, 1897, lxvii, 395.
14. **Beebe, S. P.** *Loc. cit.* (*See* ref. 12.)
15. **Vassale and Generali.** Sugli effetti dell'esterpazione delle ghiandole paratiroidee. Riv. di Patol. nerv. e ment., 1896, i, 249.
16. **Gley, E.** The pathogeny of exophthalmic goiter. Brit. Med. Jour., 1901, ii, 771.
17. **Tanberg, A.** The relation between the thyroid and parathyroid glands. Jour. Exper. Med., 1916, xxiv, 547.
18. **Jeandelize.** Insufficance thyroidienne et parathyroidienne, 1905, 45.
19. **Kendall, E. C.** *Loc. cit.* (*See* ref. 9.)
20. **MacCallum and Voegtlin.** On the relation of the parathyroid to calcium metabolism and the nature of tetany. Johns Hopkins Hosp. Bull., 1908, xix, 91.
21. **Hunziker, H.** Goiter in Switzerland. Corresp.-Blatt f. schweiz. Aerzte, Feb. 23, 1918, xlviii, 247.
22. **McCarrison, R.** The experimental production of congenital goiter. Indian Jour. Med. Research, July, 1916, iv, 183.
23. **Breitner.** Cited by Crotti. Thyroid and Thymus, 1918, p. 243.
24. **Markoe, J. W.** Discussion on goiter in pregnancy by L. F. Watson. Trans. Amer. Med. Assn., June 12, 1918; Med. Rec., June 22, 1918, xciii, 1110.
25. **Goyanes, J.** Sobre un foco de bocio y cretinismo endemicos en los valles altos del tormes y del alberche. Siglo médico, 1918, lxv, 85.
26. **Kjolstad, S.** Goiter in Norwegian province. Norsk mag. f. Laegevidensk., March, 1918, lxxix, 265.
27. **Kimball and Marine.** The prevention of simple goiter in man. Arch. Intern. Med., July, 1918, xxii, 41.
28. **Kimball and Marine.** *Ibid.*
29. **Roux, C.** Prophylaxis of goiter. Corresp.-Blatt f. schweiz. Aerzte, March 23, 1918, xlviii, 369.
30. **Hunziker, H.** *Loc. cit.* (*See* ref. 21.)
31. **Bernhard, O.** Etiology and prophylaxis of goiter. Corresp.-Blatt f. schweiz. Aerzte, Jan. 19, 1918, xlviii, 65.
32. **Crotti.** Thyroid and thymus, Philadelphia, 1918, p. 221.
33. **McCarrison, R.** The etiology of endemic goiter. Lancet, Feb. 8, 1913, i, 365.
34. **Messerle, Fr.** Le traitement du goitre par la désinfection intestinale continué. Rev. méd. de la Suisse Rom., March, 1915, xxxv, 148.
35. **Myers, E.** The use of electricity in the various forms of goiter. Northwest Med., Jan., 1916, xv, 11.
36. **Tansini, I.** Cura del gozzo col metodo di Luton. Gaz. degli osped., 1915, xxxvi, No. 1, p. 85.
37. **Sarkissiantz, A.** A propos de la "récidive" du goiter opéré. Rev. méd. de la Suisse Rom., 1917, xxxvii, 525.
38. **Wilson, L. B.** Goiter considered from the standpoint of the pathologist. Miss. Valley Med. Jour., Aug., 1918, xxv, 225.
39. **Wilson, L. B.** *Ibid.*
40. **Goyanes, J.** Sobre un foco de bocio y cretinismo endemicos en los valles altos del tormes y del alberche. Siglo médico, Mar. 9, 1918, lxv, 182.
41. **Lobenhoffer, W.** Die Verbreitung des Kropfes in Unterfranken. Mitteil. a. d. Grenzgeb. d. med. u. Chir., 1912, xxiv, No. 3, 475.
42. **Kappenburg, D. G.** Over het voorkomen van struma. Nederl. Tijdsch. voor Geneesk., Dec. 9, 1916, lx, 2079.

43. Smith, F. M. Statistical study of simple and toxic goiter at Jefferson Barracks, Mo. Jour. Amer. Med. Assn., 1919, lxxii, 471.
44. Pidcock, J. Goiter as it exists in Weber County. Northwest Med., Jan., 1913, v, 9.
45. Theisen, C. F. Acute thyroiditis as a complication of acute tonsillitis. Ann. Otol., Rhin. and Laryn., 1914, xxiii, 1.
46. Kocher. Keene's Surgery, 1908, iii, 380.
47. DeMassary, E. Thyroidite chronique avec myxedème fruste simulant la paralysie générale chez un syphilitique; guérison par de mercure et la poudre de thyroide. Bull. et mém. Soc. méd. d. hôp. de Paris, 1914, 3 sér. xxxviii, 231.
48. McCarrison, R. *Loc. cit.* (*See* ref. 33.)
49. Crotti. *Loc. cit.* p. 401. (*See* ref. 32.)
50. Beebe, S. P. The relation of pathologic conditions in the nose and throat to the origin and treatment of hyperthyroidism. Jour. Amer. Med. Assn., Aug. 29, 1914, lxiii, 769.
51. Beebe, S. P. Thyroid disease and the war. Med. Rec., Feb. 9, 1918, xciii, 237.
52. Bénard, L. La maladie de Basedow et la guerre. Bull. de l'Acad. de méd., Nov. 28, 1916, 3 sér. lxxvi, 428.
53. Léniez. Sur le goitre exophthalmique traumatique. Progrès méd., Nov. 20, 1916, 215.
54. Carter, G. The etiology of Graves's disease. Edinburgh Med. Jour., Oct., 1899, vi, 343.
55. Bénard, L. *Loc. cit.* (*See* ref. 52.)
56. Hare, H. A. The frequency of exophthalmic goiter and its frequency in the sexes. Internat. Med. Mag., April, 1898, vii, 249.
57. Curtin, R. G. Climate as an etiological factor in Graves's disease. Trans. Amer. Climat. Assn., Sept, 1888, v, 84.
58. Oesterreicher. Cited by Chamberlain, Maladie de Basedow, Paris, 1894, p. 13.
59. Putnam, J. J. Graves' disease. Sajous's Analytic cyclopedia of practical medicine, 1914, 7th Ed., v, 106.
60. Plummer, H. S. The clinical and pathological relationship of simple and exophthalmic goiter. Amer. Jour. Med. Sci., Dec., 1913, cxlvi, 790.
61. Crotti. *Loc. cit.* (*See ref.* 32.)
62. Sajous, C. E. deM. Internal secretions and the principles of medicine, 1907, ii, 1087.
63. Riesman, D. Bruit over the eyeball in exophthalmic goiter. Jour. Amer. Assn., April 29, 1916, xlvi, 1381.
64. Plummer, H. S. Trans. Assn. Amer. Phys., July 25, 1918, xxxiii.
65. Wilson, L. B. *Loc. cit.* (*See* ref. 38.)
66. Goetsch, E. Newer methods in the diagnosis of thyroid disorders; pathological and clinical. N. Y. State Jour. Med., 1918, xviii, 259.
67. Loewi, O. Eine neue Funktion des Pankreas und ihre Beziehung zum Diabetes mellitus. Wiener klin. Wchnschr., 1907, xx, 782.
68. Johnson, W. Symptoms of hyperthyroidism observed in exhausted soldiers. Brit. Med. Jour., March 22, 1919, ii, 335.
69. Evans, Middleton and Smith. Tonsillar endamebiasis and thyroid disturbances. Amer. Jour. Med. Sci., Feb., 1916, cli, 210.
70. Aikins, W. H. B. Radium therapy in hyperthyroidism with observations on the endocrinous system. Can. Pract. and Rev., Aug., 1918, xliii, 235.
71. Porter, M. F. Injection of boiling water in treatment of hyperthyroidism. Jour. Amer. Med. Assn., July 12, 1913, lxi, 88.
72. Watson, L. F. Treatment of certain types of goiter with quinine and urea injection. Texas Med. Jour., Oct., 1916-1917, xxxii, 152.
73. Plummer, H. S. The function of the thyroid gland. Trans. Med. Soc. State of N. Y., May 22, 1918; Med. Rec., Sept. 28, 1918, xciv, 567.

74. Wilson, L. B. *Loc. cit.* (*See* ref. 38.)
75. Kocher, Th. Ueber Basedow. Verhandl. d. deut. Gesellsch. f. Chir., 1911, xl, Th. ii, 617.
76. Goetsch, E. *Loc. cit.* (*See* ref. 66.)
77. Judd and Pemberton. Results of operations for exophthalmic goiter. Surg., Gynec. and Obstet., March, 1916, xxii, 269.
78. Starck, H. Indikationen zur Operation des Morbus Basedowii und Operationserfolge. Deut. med. Wchnschr., 1915, xli, No. 28, p. 822.
79. Syllaba, L. Die Prognose der Basedowschen Krankheit. Therap. d. Gegenwart, Nov., 1910, li, 484.
80. McCarrison, R. Etiology of endemic cretinism, congenital goiter and congenital parathyroid disease. Lancet, March 21, 1914, i, 817.
81. Cristiani, H. La greffe thyroidienne chez l'homme. Semaine méd., 1904, xxiv, 81.
82. Charrin and Cristiani. Greffes thyroidiennes (myxedème et grossesse). Bull. méd., Paris, 1906, xx, 630.
83. Cristiani. De la greffe thyroidienne. Recherches experimentales et cliniques. Bull. de l'Acad. de méd., 1907, lviii, 7.
84. Kummer, E. Résultat tardif d'une autogreffe thyroidienne. Rev. méd. de la Suisse Rom., 1916, xxxvi, 241.
85. Goodman, C. The transplantation of the thyroid gland in dogs. Amer. Jour. Med. Sci., 1916, clii, 348.
86. Kocher, Th. Dauerresultate der Schilddrüsentransplantation beim Menschen. Deut. med. Wchnschr., 1914, xl, 988.
87. Kendall, E. C. *Loc. cit.* (*See* ref. 9.)
88. Pool, E. H. The relation of the parathyroid system to the female genital apparatus. Surg., Gynec. and Obstet., Sept., 1917, xxv, 260.
89. Winternitz, M. C. Tuberculosis of the parathyroid gland and its relation to the occurrence of tetany in tuberculous meningitis. Johns Hopkins Hosp. Bull., 1909, xx, 269.
90. Branham, J. H. Tetany following thyroidectomy cured by the subcutaneous injection of parathyroid emulsion. Annals of Surg., 1908, xlviii, 161.

CHAPTER III

DISEASES OF THE SPLEEN

By C. H. Bunting, B.S., M.D.

Introduction, p. 273; Anatomy of the spleen, p. 274; Physiology, p. 275; Splenectomy, p. 277—Abnormalities, p. 280:—Abnormalities of size and shape, p. 280; Abnormalities of position, p. 281:—Congenital displacement, p. 281; Acquired displacement, p. 281—Traumatic lesions, p. 282:—Wounds, p. 283; Contusion, p. 283; Rupture of the spleen, p. 284—Vascular lesions, p. 285:—Chronic passive congestion, p. 285; Hemorrhages, p. 286; Infarct of the spleen, p. 286—Degenerations, p. 287:—Amyloid infiltration, p. 287—Inflammation of the spleen, p. 288:—Abscess of the spleen, p. 289; Tuberculosis of the spleen, p. 290; Syphilis, p. 291—Tumors of the spleen, p. 292:—Acute splenic tumor, p. 292; Chronic splenic tumors, p. 293:—Splenomegaly of the Banti type, p. 293; Gaucher's splenomegaly, p. 296; Tropical febrile splenomegaly, p. 296; Infantile kala-azar, p. 298; Histoplasmosis, p. 298; Cysts of the spleen, p. 299; New growths, p. 300—Bibliography, p. 301.

Introduction.—The spleen has ever been an organ of mystery. The conspicuous size of the organ, its relatively large blood supply, and its apparently close relation to the stomach, have rendered its function a fertile field for speculation. In the remote past, it has been regarded at various times and by diverse theorists as the seat of the soul, as the organ of dreaming, of melancholy and of laughter, of sleep and of the venereal appetite, as the organ that secretes the mucilaginous fluids of the joints, the organ of secretion of the atra bilis, of a fluid intended to nourish the nerves, of the gastric juice, of a humor intended to temper the alkaline character of the chyle or bile (Dunglison). Less remotely, Hewson demonstrated to his own satisfaction that the spleen manufactured the red blood-cells; Tiedemann and Gmelin considered its functions to be identical with those of the mesenteric glands; Voisin thought it furnished to the liver materials that entered into the composition of the bile; Rush considered it a diverticulum of the circulation for temporary storage of blood, while Paley, in his "Natural Theology," considered it to be merely "a soft cushion to fill up a vacuum or hollow which, unless occupied, would leave the package loose and unsteady." (Dunglison.)

While the function of the spleen may not even at the present time be fully understood, from the standpoint of clinical medicine the organ is best considered as a filter set in the blood stream. It thus bears the same relation to the blood as the numerous masses of lymphoid tissue in the body bear to the lymph. Under normal conditions, apparently, the organ filters from the blood stream the not inconsiderable number of red blood-cells which disintegrate daily in the ordinary wear and tear of life—a mechanical filtration. It also initiates the process by which the iron of the hemoglobin of these corpuscles is retained within the body—a chemical filtration. Under abnormal conditions, cells foreign to the circulation, such as nucleated red blood-cells and myelocytes, are also filtered out. The retention of such cells within the pulp spaces may add greatly to the volume of the organ. The spleen is also an efficient filter for bacteria and other parasites within the blood stream. Such a filter is not indispensable to life, as has been recognized from earliest times, and its removal is without permanent ill effects.

Set, as it is, deep within the abdominal cavity, covered by a heavy capsule, and having no lymphatic circulation, the spleen is affected by practically only such disease agencies as may be conveyed to it through the blood circulation or by such as may affect the formed elements of the blood itself. The organ commonly plays but a secondary rôle in the disease picture. Only infrequently are symptoms attributable to its lesions dominant.

The firm establishment of the fact that the spleen is not necessary to life, and the improvement in surgical technic, have removed to a large extent the treatment of its diseases from the hands of the physician and placed it in the hands of the surgeon. The excision of the organ is now performed with benefit to the patient in a large number of conditions, in addition to the so-called mechanical diseases in the treatment of which it was first applied.

Anatomy of the Spleen.—FORM AND POSITION.—The spleen is an ovoid organ, triangular in cross-section, which measures approximately 12 x 7 x 3 cm., and weighs ordinarily between 140 and 170 grams, although it may vary in weight between 100 and 200 grams in the healthy adult. The anterior border of the spleen shows a variable number of notches, usually from 2 to 4. These vary also in depth. They may be of diagnostic value when the organ is palpated in an abnormal location.

The organ lies normally in the left hypochondrium between the fundus of the stomach and the diaphragm, but comes in contact also with the tail of the pancreas and with the left kidney. The upper pole of the spleen lies about 2 cm. from the vertebral column and from this point the long axis extends obliquely, following closely the rib lines to a point about 3 cm. above the left costal border.

BLOOD SUPPLY.—The spleen receives its blood supply through the splenic artery, a branch of the celiac axis. The artery is relatively large when compared to the size of the organ. Before entering the spleen it divides into 5 or 6 branches, each of which gives off, practically at the surface of the organ, a branch to the fundus of the stomach. The corresponding splenic veins receive corresponding veins from the fundus at practically the same location. These vasa brevia of the stomach show no large anastomoses with each other, and it is thus with compression of the thin-walled veins between an enlarged spleen and a full or dilated stomach, or with obstruction of the veins by thrombosis, that gastric hemorrhage, which is of so frequent occurrence in marked splenic enlargement, takes place.

LYMPH SUPPLY.—While the majority of standard anatomies describe a superficial and a deep set of lymphatics for the spleen, careful study confirms Mall's statement that there are no lymphatics in the organ, with the exception of capsular lymphatics found only in some animals, as the ox, the pig, and the horse. Perivascular lymphatics may be traced to the hilum in man.

NERVE SUPPLY.—The nerve supply consists of medullated and nonmedullated fibers, chiefly the latter, derived from the celiac plexus and the right vagus. The fibers are distributed within the organ to a fine plexus about the arteries and to the smooth-muscle fibers within the coarser framework.

STRUCTURE OF THE SPLEEN.—Except for a narrow area along the hilum the spleen is covered by a serous membrane which overlies a dense capsule composed of white fibrous, yellow elastic, and reticulated tissue. Within this capsule are smooth-muscle fibers varying in quantity in different species of animals. They appear to be fewer in man than in some animals, notably the dog. From the capsule trabeculæ similarly composed run into the spleen substance, dividing it into lobules of approximately 1 mm. diameter. These form the anatomical units of the organ. Of these units there are in the spleen of the dog, on an average, 80,000 (Mall).

At the center of the unit lies an arteriole with its surrounding sheath of lymphoid tissue, the malpighian corpuscle. At the periphery of the lobule lie the veins in association with the interlobular trabeculæ. Between lies the red pulp. This mass is further divided by finer intralobular trabeculæ into 9 or 10 compartments corresponding to the branches of the arteriole. Within these compartments of the lobule the arteriole branches divide still further, until in the spleen of the dog, as Mall has estimated, there are approximately 500,000,000 terminal branches. Each of these branches opens freely through its terminal ampulla into the center of a small mass or cord of reticular tissue, about 50 micra in diameter, which is bounded peripherally by a venous plexus. This last unit Mall has designated the histological unit, and his investigations show that the arterial blood passes directly into this reticular pulp mass and then through it into the venous sinuses. The latter are lined by characteristic slender spindle-shaped endothelial cells which fit closely together only when there is no distention of the sinus.

Within the histological unit, the framework of the organ consists chiefly of a very delicate reticulum upon which lie the reticulo-endothelial cells, the chief phagocytes of the organ. Within its meshes are found chiefly lymphocytes and red blood-cells.

Physiology.—From the standpoint of the physiologist, the most definite facts known about the spleen, according to Howell, are in connection with its movements. After a meal, there is a slow expansion of the organ which reaches a maximum size at about the fifth hour, and is followed by a slow return to its former size. No adequate interpretation of this movement has been given. Roy has shown a further movement in the spleen of cats and dogs consisting of rhythmic contractions of the organ at intervals of about a minute. These latter movements are explained as an aid to the circulation of blood through the spleen.

From a study of the spleen in pathological conditions, and from the results of experimental investigation, the assumption made in the introductory paragraphs, that the spleen is a filter in the blood stream, seems justified. Under normal conditions, the appellation "graveyard of the red blood-corpuscles" is not inappropriate. Such a function is no mean one if we may accept Zoja's figures that one-tenth of all the red blood-cells in the body is destroyed each day, or even if we reduce the proportion to one-fortieth, as Eppinger's figures indicate. The reticulo-endothelial phagocytes undoubtedly play a large part in this filtration and also in the catabolism of the hemoglobin and the retention of its iron for further use in the body. It seems probable, however, that the liver and not the spleen plays the greater rôle in the metabolism of hemoglobin set free in the blood stream by complete hemolysis.

Observations by the author indicate that this filter is also operative for excess leukocytes in the blood stream after a leukocytosis. This is comparable to the filtration by the lymph-nodes of leukocytes from the peripheral lymph returned from a field of inflammation. Under more markedly pathological conditions, this filtration extends to other cells which are foreign to the circulation, such as myeloblasts and myelocytes in the leukemias, as is shown by the vast accumulation of these cells in the spleen pulp. Malarial parasites, malarial pigment, and the Leishman-Donovan parasites are also held up in the spleen. Ozaki has shown that when removed from the body the spleen is not as effective a mechanical filter for bacteria as the kidney, but that within the living body it is much more effective. This increase in effectiveness he attributes to the activity of the endothelial phagocytes on the spleen reticulum.

Although the spleen functions during early fetal life as a blood-forming organ, there is no evidence that it so serves during normal adult life except in so far as lymphocytes are formed in the malpighian corpuscles as in other lymphoid tissue. Under pathological conditions, as in the severest anemias in man and in those produced in animals, the organ may revert to its embryological function of red blood-cell production. It must be emphasized, however, that the mere presence of nucleated red-cells within the spleen pulp is no evidence of red blood-cell manufacture in the organ. The only satisfactory evidence of such manufacture is the presence within the sinuses of blood-cell groups with the arrangement characteristic of the adult red marrow.

Splenectomy shows that the spleen plays no essential part in the nitrogen metabolism of the body, at least no part which cannot be replaced by rapid compensation on the part of other organs. The richness of the spleen in purin bases and the presence of an enzyme adenase led at one time to the supposition that the organ might play an important part in the metabolism of these substances. In the light of subsequent work this view has not been maintained.

One cannot dismiss the consideration of the function of the spleen as an organ for the removal of injured red blood-cells without touching upon the question of "hypersplenism" under pathological conditions. The improvement after splenectomy in the condition of patients suffering from various types of anemia has led a group of investigators, among whom Eppinger may be cited, to the conclusion that in these conditions the phagocytes of the spleen have been stimulated in some way to an increased activity toward the red-cells. This hypersplenism is held to be analogous to hyperthyroidism or to overactivity of the glands of internal secretion in general. The opposing view regards the filtration action of the spleen as of a more passive character, and insists that only injured red blood-cells are subject to phagocytosis. Following such a view, the beneficial results of splenectomy in certain diseases would be interpreted not as due to the removal of an organ that had been perverted to activity hostile to the body, but possibly as due to the removal with the spleen of some noxious agent which was producing an injury to red-cells within the spleen substance. Sufficient evidence has not yet accumulated to allow of a final decision in this controversy.

Splenectomy.—Lesions of the spleen are either of such a character as to require no special treatment, or of such a nature that surgical treatment alone is of value. Owing to the vascularity and friability of the organ, splenectomy is the operation of choice in the majority of cases where surgical intervention is demanded. This point of view has received final acceptance only after repeated demonstration that the removal of the spleen results in no permanent disability in animals or in man.

The history of splenectomy affords an interesting chapter in the history of surgery, leading back into medical antiquity. The ancients were acquainted with the fact that the spleen was not a vital organ, if we may accept Pliny's affirmation that runners were accustomed to have their spleens removed to improve their wind, and with no greater harm resulting than the loss of their laughter. Although from the 16th century on, numerous successful splenectomies, usually for prolapse of the organ through an abdominal wound, were reported, it was not until late in the 19th century that the operation was performed with any degree of frequency. Thus, while Adelman collected but 53 cases of splenectomy in 1887, Johnston was able to analyze the results of 708 operations in 1908, and there has been a rapid increase in the number of cases since that time. The operation has been performed, not always justifiably, for a great variety of conditions, classified by Balfour as follows:

1. Anatomical anomalies and injuries
    - (*a*) Malposition and malformation
    - (*b*) Traumatism
    - (*c*) Accessory spleens
2. Tumors, cysts, etc., and new growths
    - (*a*) Abscess
    - (*b*) Angioma
    - (*c*) Cysts
        - (1) Simple
        - (2) Dermoid
        - (3) Hydatid
    - (*d*) Sarcoma and carcinoma
3. Chronic splenomegaly occurring in diseases of bacterial or protozoan origin
    - (*a*) Tuberculosis
    - (*b*) Syphilis
    - (*c*) Malaria
4. Diseases in which the spleen has been proved to be the controlling etiological factor
    - (*a*) Splenic anemia
        - Adults
        - Children
    - (*b*) Hemolytic jaundice
        - Congenital and familial
        - Acquired
5. Conditions with which the spleen is intimately associated primarily or secondarily
    - (*a*) Hepatic cirrhosis
    - (*b*) Gastro-intestinal hemorrhage of unknown cause
    - (*c*) Thrombophlebitis of splenic and portal veins
6. Primary "endothelioma" of the spleen
    - (*a*) Gaucher's disease
7. Diseases of the blood and blood-forming organs
    - (*a*) Pernicious anemia
    - (*b*) Splenomedullary leukemia
8. Unclassified splenomegaly
    - (*a*) Idiopathic splenomegaly
    - (*b*) Chronic septic spleen
    - (*c*) Splenomegaly with eosinophilia
    - (*d*) Tropical splenomegaly

While the operation is one not to be undertaken lightly, with a proper selection of cases and with an acceptable surgical technic, the mortality should be low. Thus, while Johnston's analysis of the total 708 collected splenectomies before 1908 shows a mortality of 27.4 per cent., his analysis of 235 justifiable splenectomies performed between 1900 and 1908 gives a mortality of 11.5 per cent., and he further records 55 operations for ectopic spleen and simple cyst of the spleen with but a single death. In so grave a condition as pernicious anemia, the 153 cases of splenectomy collected by Krumbhaar show a mortality of 19.6 per cent., or, better, of 11 per cent. where the hemoglobin was above 30 per cent. at the time of operation. In the Banti type of splenomegaly, where the technical difficulty of the operation is great owing to the size of the organ and the frequency of vascular adhesions, the operative mortality at the Mayo Clinic in all stages of the disease is but 9.6 per cent. of 31 cases (Balfour).

It is not within the scope of this article to enter into details as to the justifiableness of the operation or into the surgical technic to be employed. Each case must be judged by itself. It may be said in general, however, that the very high mortality resulting from splenectomy in leukemia would seem not to justify operation in that disease, especially since *x*-ray or radium treatment either over the spleen itself or over the long bones will cause a marked diminution in size of the organ. In the pre-ascitic stage of Banti's disease the operation is curative. In pernicious anemia the best results have occurred in those cases with large spleens and a good blood-picture, but the operation is ameliorative only, not curative. The mortality is high in rupture of the spleen because of the gravity of the patient's condition, but immediate operation is demanded because of the almost uniform fatality in non-operative cases. In these over 50 per cent. of the deaths occur within an hour after the injury.

The postoperative physiology of spleenless men and animals is of interest in indicating to some extent the part played by the gland in the organ complex of the body.

Paton's study of the urinary nitrogen, sulphur, phosphoric acid, and chlorin in the splenectomized dog showed that there is no essential difference in the course or nature of the metabolism either during fasting or after feeding with the ordinary proteids of flesh or vegetable foods or with foods rich in nucleins. This has been confirmed by the studies of Goldsmith and Pearce.

Asher and his associates have shown an increased loss of iron from the body in both animals and man after splenectomy. Austin and Pearce, however, found but a temporary increase in iron elimination, and in only three out of five splenectomized dogs. They are unwilling to assign to the spleen any preponderant influence in iron conservation.

King demonstrated an increase in the total fats and cholesterin in the blood after splenectomy, a finding which Dubin and Pearce do not confirm.

Musser and Krumbhaar have shown that following splenectomy in dogs there is an anemia of variable grade which develops quickly and reaches a maximum in from 3 to 6 weeks, with a full return to a normal count in from 5 to 10 months. There is also a marked postoperative neutrophil leukocytosis which reaches its maximum in 24 hours, but persists in varying degree for weeks and even months. An early absence of eosinophils is followed by an eosinophilia, often of striking degree. There is also an early decrease in the large forms of leukocytes, followed by an increase.

The resistance of the red-cells to hypotonic salt solution is increased after splenectomy.

Warthin has shown that following splenectomy compensation for absence of the organ is made by the hemolymph glands and later by the ordinary lymph-nodes. This compensation he believes to be excessive at first, resulting in the postoperative anemia and in a compensatory extension of red bone-marrow replacing the fatty marrow. These findings are confirmed by experiments of Pearce and his co-workers, and by clinical cases.

Whatever the function of the spleen, its absence is soon compensated for, and spleenless men are apparently normal individuals.

ABNORMALITIES

Abnormalities of Size and Shape

Many abnormalities in size and in shape of the spleen have been noted, but they are of pathological rather than of clinical significance, as they afford no symptoms during life and are first discovered at postmortem examination.

The most frequent abnormality is a variation in the number and in the depth of the notches on the anterior border of the organ. These may be absent or may be increased to eight or more. They may be of insignificant depth, or may be so deep as to divide the organ completely, producing a bilobed or multilobed spleen.

Double spleens of approximately normal size and shape have been described in man and in animals. Two equal and normal-sized spleens have been observed recently in a rabbit in this laboratory.

In about 10 per cent. of postmortem examinations accessory spleens are found. These are usually few in number and of small size and lie close to the hilum of the organ. In several reported cases, however, from 40 to 50 have been found more widely distributed over the peritoneal surfaces, and in the remarkable case of Albrecht, it was estimated, there were 400 accessory spleens. In this case the principal spleen was of about the size of a walnut, and the accessory ones, varying in size from that of the head of a pin to that of a pea, were scattered practically throughout the abdominal cavity. Such a picture might easily, in case of abdominal exploration, lead to the mistaken diagnosis of peritoneal implantation-metastasis of a malignant tumor.

Atrophy of the spleen in old age is to be regarded as physiological. Diminutive spleens in young adults, without signs of previous disease of the organ, have been described by various authors. The spleen of Calvert's case weighed but 2.1 grams and was imbedded in a compensatory growth of adipose tissue.

Rokitansky states that the spleen is generally absent in acephalous monsters, and is occasionally found wanting together with the stomach or the fundus of the stomach. The entire absence of the spleen without other anomaly than the failure of proper development of the splenic artery has been reported by a number of authors. Of these reported cases, the more recent ones of Hodenpyl and of Sternberg were adults, and the careful dissection by these authors seems to establish the occurrence of congenitally spleenless men beyond a doubt. Compensatory enlargement of the lymph-nodes may be prominent in these cases.

ABNORMALITIES OF POSITION

Congenital Displacement

In complete *situs transversus*, the spleen is found in the right hypochondrium. In other malformations, it may be displaced as a result of being caught in some of the complex movements which take place in the abdominal cavity during fetal life. In congenital defects of the diaphragm, the organ may be found in the thoracic cavity.

Acquired Displacement

Synonyms.—Wandering or floating spleen; ectopic spleen; dislocation of spleen.

Etiology.—Wandering spleen is more common in women than in men, and is more often found in the adult than in the young. The factors leading to its dislocation vary. The great factor apparently is increased weight of the organ. While any of the causes of splenic enlargement may be operative, chronic malaria is the most common cause. Aside from enlargement, a congenital laxity or abnormal length of the splenic ligaments may be a cause, or an acquired laxity as a part of a general visceroptosis with lax abdominal wall.

Symptomatology.—GENERAL SYMPTOMS.—In those who are not sensitive to slight bodily discomforts, dislocation of the spleen may give no symptoms, and the accidental discovery of an abnormal lump or tumor mass in the abdomen may be the first indication of the condition. In the ordinary patient, simple dislocation of the spleen usually causes a dragging sensation referable to the upper part of the left side of the abdomen, with at times sharper pains in the same region. The symptom-complex, however, varies, depending upon the size of the dislocated organ, upon its location in the abdominal cavity, and upon its relations to other organs. Where the condition is but a part of a general visceroptosis, the patient may show a train of symptoms usually grouped under the term neurasthenia. Pressure of the enlarged, dislocated spleen, or adhesions between it and other organs, may result in constipation, even in intestinal obstruction, in irritation of the bladder with frequent micturition, in interference with the uterus, especially in pregnancy, or, rarely, by pressure on the kidney, in hematuria. Nausea and vomiting, even vomiting of blood, may occur as the result of interference with the circulation of the fundus of the stomach. Torsion of the pedicle of the ectopic spleen leads to acute attacks of sharp pain, nausea, vomiting, chills, and fever. (*See* Infarction of Spleen.)

Physical Findings.—Physical examination of the patient reveals a tumor mass which may lie in any part of the abdominal cavity, and which not infrequently extends below the pelvic brim. The mass usually lies relatively superficially, and it may by palpation be found to have the shape of the enlarged spleen. Very commonly the notches of the anterior edge may be made out. Absence of splenic dulness in the normal location for it may be noted.

Laboratory Findings.—Laboratory findings are negative in simple ectopic spleen. Blood investigation may show a preëxisting leukemia, or malarial infection.

Diagnosis.—While the diagnosis of wandering spleen is easily made from a textbook standpoint, in practice it appears to be made relatively infrequently before operative incision of the abdomen. A superficially placed, notched tumor of splenic shape, especially with absence of normal splenic dulness, establishes the diagnosis in the presence of suitable symptoms. Often, however, the spleen is so rotated that its shape may not be clearly made out and its notches cannot be felt. In the pelvis, it is most often diagnosed either as an ovarian or uterine tumor or pelvic abscess; in the flank, it is not uncommonly diagnosed as a floating kidney, especially if it lies on the right side, or if it becomes suddenly enlarged as the result of torsion of its pedicle.

Complications.—The complications are those due to vascular obstruction after twisting of the pedicle (necrosis), those due to adhesions to other organs (intestinal obstruction, etc.), and those due to interference with the gastric circulation (hematemesis).

Treatment.—The treatment of simple wandering spleen is surgical and **splenectomy** is the operation of choice. **Splenopexy** has been tried, but is difficult owing to the vascularity and friability of the organ. In some cases it has resulted in late postoperative symptoms from adhesions, and, in one case, from a subsequent twisting of the pedicle. In wandering leukemic spleen, **x-ray** or **radium** should first be tried, after which removal of the spleen in its reduced state may be considered.

Prognosis.—The operative risk in splenectomy for simple ectopic spleen or ectopic spleen with twisted pedicle is of the slightest, and the operation is, of course, curative. In cases without operation the liability to complications is great, though the prognosis cannot be considered grave.

Pathology.—Even without preëxisting lesion the dislocated spleen is seldom found to be normal. Its dependent position in the abdominal cavity usually leads to interference with venous return, and thus to chronic passive congestion of the organ. With torsion of the pedicle, necrosis of the entire organ may be found.

TRAUMATIC LESIONS

The traumatic lesions of the spleen include penetrating wounds (gunshot or stab-wounds), contusion and rupture.

WOUNDS

Berger has collected 150 cases of wounds of the spleen, of which 106 were bullet wounds and the rest stab-wounds or cuts. Owing to its location the organ is seldom the only one injured in such wounds, and thus contributes only in part to the clinical picture. The symptoms attributable to spleen injury are virtually those of spleen rupture (q.v.); the prognosis is almost as unfavorable, and the treatment is surgical. If the spleen is badly injured, splenectomy should be done. If, upon exploration, hemorrhage is found to have ceased, the organ may safely be left.

CONTUSION

Contusion of the spleen is the result of trauma insufficient in degree to produce rupture.

Etiology.—The predisposing cause in many cases is malaria. The provoking cause is a blow or a fall.

Symptomatology.—At the time of the accident there may be sharp pain in the splenic region. This pain may continue with the stretching of the capsule due to the hemorrhage beneath.

PHYSICAL FINDINGS.—The spleen may be demonstrably enlarged and may project below the costal border, but usually its increase in size is to be made out only by the increased percussion area. Many cases have shown a fever of the quotidian type, due, it is thought, to a preëxisting malarial infection.

Diagnosis.—The diagnosis rests upon a history of trauma and pain in the splenic region with increase in size of the organ and absence of the signs of hemorrhage as seen in rupture.

Complications and Sequelæ.—The contused spleen may rupture some days after the trauma as the result of the capsule giving way under the pressure of continued hemorrhage. Commonly, the hemorrhagic area is converted into the so-called blood-cyst, or into a secondary serous cyst, through partial encapsulation and organization. Less frequently, infection and abscess formation occur at the site of the hemorrhage. In very rare cases the spleen is so injured that necrosis takes place, followed by infection which may extend to the peritoneum.

Treatment.—While moderate contusion of the spleen may heal without treatment, the patient should be put to bed and be carefully watched for any evidence of extension of the hemorrhage and consequent rupture of the organ, or of infection. In case of the appearance of alarming symptoms, surgery should be resorted to. **Splenectomy** may be required.

Prognosis.—The prognosis in mild cases is good. Prompt surgical intervention in unfavorable cases gives a high percentage of recoveries.

Pathology.—The organ shows rupture of its internal fibers with hemorrhage of variable extent, but without rupture of the capsule.

RUPTURE OF THE SPLEEN

Rupture of the spleen may be spontaneous in a pathological organ, or traumatic in either a normal or a pathological organ.

Etiology.—Traumatic rupture is more frequent than spontaneous rupture. Age has little bearing upon the occurrence of rupture except that the greater number of cases occur before the fortieth (40th) year, after which it is possible that the gradual atrophy of the spleen and the increase in its fibrous constituents reduces its liability to injury. The youngest case reported by Simpson was of a new-born child who fell to the floor during labor. Although the pathological spleen is more liable to rupture than the normal one, about 55 per cent. of traumatic ruptures have been in normal spleens. This is undoubtedly due to the fact that the pathological conditions most conducive to rupture are such as to confine the patient to bed and thus reduce the liability to trauma. The most common predisposing factor in traumatic rupture is malaria, but occasionally some other infection which produces an acute splenic tumor, such as typhoid fever, plays a part.

Spontaneous rupture is most common in malaria, but in this disease is not frequent. Noland and Watson note three instances in 30,000 malarial cases treated in the Colon Hospital. Rupture occurs also in typhoid fever, leukemia, congenital syphilis, tuberculosis, and in other infections in which there is a splenic tumor of such extent that the capsule of the organ is stretched almost to the bursting point, and the abdominal tension caused by a cough or a sneeze or a simple turning in bed produces sufficient increased strain to cause the break.

Symptomatology.—The symptoms of ruptured spleen are collapse and sharp pain in the splenic region. The pain may radiate to the left shoulder and is usually described as deep-seated. There may be slight nausea and vomiting. Increased thirst is usually present.

PHYSICAL FINDINGS.—In recent rupture the patient is pale, cold, anxious-looking, and in collapse, with small, thready pulse and shallow, rapid respirations. Abdominal rigidity is present and is most marked in the upper part of the left rectus, where there is tenderness upon pressure. Dulness may be noted in the flank if the hemorrhage is extensive. In late cases the abdomen becomes distended, fever is present and signs of early peritonitis may be noted.

LABORATORY FINDINGS.—A decreasing red blood-cell count will be found as the decrease in blood volume is made up by absorption of fluid from the tissues. The leukocytosis of hemorrhage will gradually develop and will be intensified with the onset of infection.

Diagnosis.—With a history of trauma and with the signs and symptoms indicated, the diagnosis should be evident. In spontaneous rupture during the course of some acute disease, diagnosis may be more difficult. Yet in either case a fine diagnosis is unnecessary, as the gravity of the patient's condition, with abdominal localization of symptoms, is such as should lead to prompt exploration.

Complications.—Traumatic rupture of the spleen is often complicated by rupture or injury of other abdominal organs, or by fracture of ribs or other bones. In fact, in abdominal trauma, the liver is more often ruptured than the spleen (in a proportion of 37 to 20), and the kidney practically as often as the spleen. Injury to the pancreas or rupture of the intestine or stomach may be associated with splenic rupture.

Sequelæ.—In those cases of untreated rupture which survive several days, infection is apt to occur and result in either abscess or peritonitis or both. Such infections, according to Berger, account for about 10 per cent. of the deaths from rupture.

Treatment.—In view of the high non-operative mortality, temporizing **medical** treatment should not be attempted. Immediate surgical intervention with **splenectomy** offers practically the only hope for the patient, except in the rare instances in which some old adhesion has limited the hemorrhage.

Prognosis.—Without operation the mortality is extremely high, being 92.3 per cent. of the 220 cases collected by Berger, and in the recovered cases a doubt which Berger recognizes might be justified, that rupture had not been properly differentiated from contusion with subcapsular hemorrhage. Of the fatal cases (Berger), 51.8 per cent. died within the first hour and 86.3 per cent. during the first day. The mortality in cases treated by splenectomy is also high. In 150 cases of traumatic lesions of the spleen, including wounds and rupture, so treated, Johnston found a mortality of 35 per cent.

Pathology.—The rupture is a break of varying extent and depth through the capsule and deeper tissues of the spleen, with free hemorrhage. The break more often affects the lower part of the spleen than the upper, the inner surface rather than the outer, and more often runs across than parallel to the long axis of the organ. There may be a single split, multiple fissures, or a stellate fissure.

VASCULAR LESIONS

The active hyperemia of the spleen occurring in certain acute infections and intoxications is discussed under acute splenic tumor (q.v.).

Acute passive congestion occurs as a result of the overloading of the right heart during strenuous exercise, as running, and it accounts for the pain in the left side often felt in such circumstances. It is without clinical significance.

CHRONIC PASSIVE CONGESTION

Chronic passive congestion results from any obstruction in the portal or pulmonary circulation, or from general cardiac incompetence with generalized passive congestion. The spleen is seldom sufficiently enlarged to give symptoms or to lead to difficulties in diagnosis. In this condition the organ merits the older designation "cyanotic induration."

It is of a deep purplish-blue color and very firm. The capsule and the fibrous elements of the organ are increased, the walls of the venous sinuses thickened, and the sinuses congested. The arterioles often show hyaline degeneration of their inner elastic lamellæ due apparently to decreased oxidation.

HEMORRHAGE

Hemorrhages in the spleen occur in various infections and in trauma (q.v.).

INFARCT OF THE SPLEEN

Infarcts of the spleen may be small, single or multiple, or may be of the entire organ.

Etiology.—The most common cause of smaller infarcts in the spleen is embolism of the splenic artery in some of its branches. Based upon evidence of pathological effects as seen postmortem, the splenic artery is the third in order of frequency of embolic processes, being exceeded only by the pulmonary and renal arteries (Welch). The emboli are usually portions of vegetations from the heart-valves. Thrombosis of the splenic arteries or veins may also result in infarction. Necrosis of the whole spleen may result from thrombosis of the main splenic artery or vein or both, or from torsion of the pedicle of the spleen, resulting in occlusion of the vessels. More rarely, it may result from embolism of the main splenic artery, or from occlusion of the artery or vein by pressure due to tumors.

Symptomatology.—GENERAL SYMPTOMS.—Single or multiple small infarcts of the spleen may occur during the course of an infectious endocarditis without symptoms being noted by the patient. In other cases, pain in the region of the spleen may occur at the time of the embolism which causes the infarct. There may also be tenderness over the enlarged spleen. Chills, with intensification of an existing febrile reaction, may indicate an inflammatory process in the infarcted area resulting from an infected embolus.

The symptoms of infarction or necrosis of the whole spleen, according to Nuzum, who has collected 28 cases in addition to 4 of his own, may be summarized as pain and tenderness in the left hypochondrium, enlargement of the spleen, occasional fever, and the vomiting of blood. Early, the pain may be diffuse over the abdomen, but later localizes in the splenic area. It may vary from a dull ache to a sharp colic, and may radiate to the left shoulder. The enlargement of the spleen may come on in a few minutes and may be of marked degree. Hemorrhage from the stomach occurs apparently when the infarction is due to thrombosis of the splenic vein or to its occlusion by torsion or pressure. The hemorrhage may be fatal.

PHYSICAL FINDINGS.—Enlarged spleen, with tenderness on deep pressure, may be found. A peritoneal friction-rub may be heard over the spleen in cases in which an infectious process has extended to the capsule.

Complications and Sequelæ.—Infarct of the spleen is in itself practically always a complication of an existing cardiovascular malady. The infarcts from bland emboli may undergo organization, as shown by the depressed scars often found at postmortem examination. With infected emboli, abscess formation in the necrotic area of the infarct is common. The infection may extend through the capsule to the peritoneum and lead to a localized or to a more general peritonitis.

The totally-infarcted spleen may undergo autolytic softening until it resembles a sac of pus, or it may become infected and be converted into an abscess.

Treatment.—The pain in infarction may be so severe as to require **sedatives.** Otherwise, treatment in case of small infarcts is unnecessary, unless a diagnosis of supervening abscess is made, when either **drainage** or **splenectomy** should be done.

Prognosis.—The prognosis in infarction is difficult to separate from that of the disease in which it occurs. Infarction due to bland emboli apparently does not increase the gravity of the patient's condition. An infected infarction, however, adds to the situation another focus of infection, which may lead to fatal results. Infarction of the whole spleen is grave and usually fatal unless there is operative intervention.

Pathology.—Infarct of the spleen, as of other organs, is to be recognized by a wedge-shaped area of necrosis involving the area supplied by the end vessel obstructed by the embolus or by the thrombus. In the spleen, the infarct may be white or red, anemic or hemorrhagic, depending somewhat upon the density of the organ at the time of infarction. The anemic infarct shows an outer red border of congestion and hemorrhage and an inner white line formed by the advancing wave of leukocytes attracted toward the necrotic tissue. According to Karsner and Austin, in experimental infarction of the dog's spleen all anemic infarcts are early hyperemic, then hemorrhagic, and only late become pale from coagulative necrosis. Organization processes are in evidence within four days. When the process is completed, a depressed somewhat angular scar is left. With infection, abscess cavities may replace the necrotic areas.

DEGENERATIONS

AMYLOID INFILTRATION

Amyloid infiltration of the spleen is the only one of the so-called degenerations of the organ which may be of clinical significance.

Etiology.—Amyloid infiltration occurs chiefly in cachectic individuals, the subjects of chronic suppuration, especially in the neighborhood of bone or cartilage. It is thus found commonly in chronic osteomyelitis, and in tuberculosis of the lungs with cavity formation, or in tuberculosis of bones and joints. It may occur in chronic ulcers of the skin or of the intestine. Amyloid is found in tertiary syphilis without demonstrable suppuration and may rarely be found in cancer, leukemia and other conditions. It is not uncommonly found in the liver of horses used for the development of diphtheria antitoxin.

Amyloid is a compound proteid consisting of chondroitin-sulphuric acid combined with a protein molecule. Apparently the acid is conveyed through the blood stream and unites with the proteid in the perivascular spaces, *in situ*. It is claimed that a *tertium quid*, a ferment, possibly, is required to complete the union. This, Davidsohn thinks, is elaborated in the spleen, for as a result of experimental work in splenectomized animals, he was unable to produce amyloid by means which were successful in the control animals. In human pathology, the spleen is nearly always involved if amyloid is found in any organ.

Symptomatology.—There are no especial symptoms to be attributed to the amyloid spleen unless its size is sufficient to produce a sensation of weight and dragging in the left hypochondrium. With marked increase in size, there may be pressure symptoms upon neighboring organs. Generally the presence of a firm mass projecting below the costal border is all that may be noted.

PHYSICAL FINDINGS.—Examination of the abdomen will reveal a firm, spleen-shaped tumor projecting below the left costal border. Rarely the tumor may extend across the midline toward the right iliac fossa, and the diagnosis from other splenomegalies must be made. Leukemia enlargement may be excluded by the blood-picture. The finding in the patient of a sufficient cause for amyloid, and signs of involvement of the liver and kidney should lead to a proper diagnosis.

Treatment.—The splenic lesion requires no treatment. Attention should be directed to the underlying cause of the condition.

Prognosis.—Involvement of the spleen by amyloid adds nothing to the gravity of the patient's condition.

Pathology.—Amyloid may be deposited in the spleen in one of two locations: in the malpighian corpuscles, giving the so-called sago spleen, or about the venous sinuses of the pulp, forming the diffuse amyloid spleen. The sago spleen is usually not much enlarged. On section, it shows translucent, waxy bodies, resembling boiled sago or tapioca, which replace the malpighian corpuscles. These give the typical mahogany reaction with iodin solutions. The diffuse amyloid spleen is usually enlarged, sometimes considerably so, and is firm to the touch. On section, the pulp is found to be increased and firm, and it has a paler appearance than the normal, with a marked translucency.

INFLAMMATIONS OF THE SPLEEN

The acute splenic tumor occurring in so many infectious diseases is not to be regarded strictly as an infection of the organ, though organisms may be present in it. (*See* Acute Splenic Tumor.) The spleen is not diffusely affected by inflammatory processes. Localized abscesses occur, and several of these may ultimately coalesce, converting the whole organ into a single abscess cavity.

Abscess of the Spleen

Synonym.—Acute suppurative splenitis.

Etiology.—Abscess of the spleen, though not frequently seen, is by no means a rare lesion. The exciting cause may be any of the pyogenic bacteria, with the apparent exception of the gonococcus, which has not yet been recovered from such a lesion. The route of infection is practically always by the blood stream, though very infrequently the organ may be infected by extension from a neighboring focus. Commonly, the organisms are conveyed to the spleen in septic emboli from vegetations on the heart-valves in acute endocarditis, and one finds, usually, numerous subcapsular abscesses replacing the infarcted areas. The condition is then usually only part of a general pyemia.

Where the lesion in the spleen is the only abscess found, the organisms may reach the spleen from some remote, obscure focus of infection, or from some obvious suppurative process, as in the pelvic organs or in the appendix. Almost any lesion of the spleen may be the predisposing factor which causes the localization of the suppurative process in it. The most common lesions, however, are traumatic injury, malaria (23 of 65 cases collected by Spear), typhoid fever, relapsing fever, and, rarely, yellow fever. Echinococcus cysts are not infrequently converted into abscesses by secondary infection.

Symptomatology.—The symptoms of abscess of the spleen may not be distinctive. Commonly the symptoms are pain and tenderness in the splenic region, and febrile reaction. The pain may radiate to the left shoulder. With involvement of the diaphragm and extension to the pleura, pain on respiration may be felt, and limitation of left-sided movement during respiration may be noted. The fever may be of the intermittent or the remittent type. Nausea and vomiting and diarrhea are not infrequently present.

Physical Findings.—The spleen is always enlarged but may not be sufficiently so to be palpated below the costal border. At times it may be enormous, and a large fluctuating mass may be palpated in the left side of the abdomen. A friction-rub may be heard when there is an extension of the inflammation to the serous covering of the spleen.

Laboratory Findings.—A sharp neutrophilic leukocytosis is found unless the patient is in such a grave condition that the bone-marrow is unable to react.

Diagnosis.—Where abscess of the spleen is but part of a general pyemia, the condition may be unrecognized. In the so-called solitary abscess, a history of focal infection, infectious disease, or trauma, with the presence of a large spleen, with or without fluctuation, fever, leukocytosis, and pain in the splenic region, should lead to the diagnosis. Aspiration of the tumor gives a positive diagnosis, and has apparently been practiced repeatedly without untoward effect (Elting), although the method has been subject to criticism. It may be difficult to diagnose between abscess of the spleen and subphrenic abscess.

Complications.—Abscess of the spleen may lead to localized or to general peritonitis or to left-sided pleurisy. The organ may become adherent to a neighboring viscus and evacuate into it. Rupture may take place into the stomach, intestine, kidney, pleural cavity, lung, or through the abdominal wall to the exterior.

Treatment.—The treatment of abscess of the spleen is surgical. The choice of operation lies between **splenectomy** and **splenotomy with drainage**, depending upon the relation of the organ to other viscera, or upon its fixation by adhesions in a position difficult for removal. Elting and Johnston prefer **incision and drainage**, though the latter reports 9 cases treated by splenectomy with but a single death. This occurred 3 months after operation in a patient with a streptococcus infection.

Prognosis.—Without operation the prognosis is grave, as the process in the spleen is often but a part of a general pyemia. Even when it is not, the mortality without operation is very high, in fact almost uniformly fatal, although cure through spontaneous evacuation of the abscess has been reported. With operative treatment the mortality is less than 25 per cent. It is apparently lowest in post-typhoid abscess.

Pathology.—The abscess may be single or there may be many. They may be microscopic in size or may contain several liters of pus. The whole organ may be converted into a pus sac.

Tuberculosis of the Spleen

In any dissemination of tubercle bacilli through the blood, the spleen is certain to be involved, for, as Rokitansky pointed out, one finds by postmortem examination that tuberculosis affects the spleen only less frequently than it affects the lungs and lymph-glands. This involvement is usually without clinical significance.

In a limited number of cases, however, the tuberculosis of the spleen dominates the clinical picture, and is often apparently the only demonstrable tuberculous lesion in the body. Winternitz has collected 51 such cases and designates them "primary tuberculosis of the spleen," although recognizing that the organ is affected metastatically through the blood stream from some remote portal of entry.

Etiology.—The greatest number of cases occurs between the twentieth and fortieth year, but cases are recorded as early as the first year and as late as the eightieth. Sex is of no etiological importance. The organ is affected metastatically through the blood stream from some older focus elsewhere in the body. The cause of the splenic susceptibility is not known.

Symptomatology.—The splenic involvement may occur with acute and severe symptoms, as fever, sweating, collapse, back-ache, and increase in size of the spleen. Commonly, the *onset* is more gradual, with pain in the splenic region, swelling of the spleen, loss of weight, weakness, and lassitude. There may also be gastric and respiratory symptoms from pressure of the enlarged spleen.

PHYSICAL FINDINGS.—The spleen is enlarged and is usually firm.

The difference in density between coagulated tubercles and intervening pulp may give the tumor a nodular feeling. Evidence of tuberculosis may be found in the lungs or in the lymph-glands.

LABORATORY FINDINGS.—The red blood-cell count may be normal, or moderately decreased, or even increased. The latter was present in 6 of Winternitz's cases, the count in the most marked polycythemia being 8,200,000 cells per cu. mm. As a rule, the leukocytes are not increased.

Diagnosis.—The diagnosis may be difficult. The history of the patient, the enlarged, tender, and painful spleen, intermittent fever, and the presence of other tuberculous lesions, should establish the diagnosis. The tuberculin reaction may help. The added presence of polycythemia would serve to confirm the diagnosis.

Complications.—In these cases, the splenic lesion is not the only tuberculous lesion in the body. Quiescent or active tuberculosis of the lungs, and tuberculosis of the liver and lymph-glands are most commonly associated. Extension from the spleen to the peritoneum is relatively frequent.

Treatment.—**Splenectomy** is the only treatment of value in the cases in which the splenic lesion dominates the clinical picture. This should be followed by the establishment of a regimen suitable for a tuberculous patient.

Prognosis.—Johnston reports 9 cases treated by splenectomy between 1890 and 1908 with one death. Without operation the condition is uniformly fatal.

Pathology.—The spleen may vary in size from approximately the normal to 4,000 grams. It usually shows numerous massive tubercles or large caseous masses, with some hyperemia of the pulp, and a variable amount of fibrosis. Some of the tuberculous masses may soften and be converted into degenerative cysts.

SYPHILIS

In the secondary stage of acquired syphilis, there may be a splenic tumor. In the tertiary stage, the organ may be the seat of gummata, but this is a relatively infrequent lesion. When present, the gummata are often large and may be associated with fibrosis of the organ and a capsulitis that results in adhesions to the diaphragm, body wall, or neighboring viscera. Amyloid infiltration may occur in the tertiary stage.

In congenital syphilis, the spleen is usually enlarged and may be the seat of fibrous changes. Gummata and amyloid infiltration may occur as in acquired syphilis. Gummata, however, are rare.

The splenic lesions are only rarely of clinical importance in cases of syphilis.

TUMORS OF THE SPLEEN

ACUTE SPLENIC TUMOR

In a variety of acute infections and intoxications there occurs a uniform enlargement of the spleen, commonly designated an acute splenic tumor. The enlargement is usually moderate, but is, in the majority of cases, of sufficient extent to render the lower pole of the organ palpable below the costal border. Not infrequently the enlargement is extreme. When examined postmortem two types of acutely enlarged spleens are seen. The one is of a deep purplish-red color and is usually designated an acute hyperemic splenic tumor; the other is grayish-purple and is termed a hyperplastic tumor. Histological examination shows that the two types are not essentially different lesions, but that in the former, hyperemia merely preponderates over the hyperplasia of the cells of the organ, while the condition is reversed in the latter. In the acute splenic tumor, the capsule is not thickened, but is greatly stretched. Upon section of the organ, the spleen pulp is found greatly increased in amount. It is soft in consistency and at times almost diffluent. Histological examination shows the pulp spaces, as well as the venous sinuses, widely dilated by an infiltration by red blood-cells and in some cases by leukocytes and by the presence of an increased number of splenic pulp-cells. Endothelial phagocytes containing red-cells may be numerous. These are the "red blood-corpuscle carrying cells," so numerous in the typhoid spleen. The malpighian corpuscles may or may not show hyperplastic change, depending upon the character of the infection present. In addition to this diffuse process in the spleen, certain lesions specific to the infectious agent may be found, as, for example, focal necroses in typhoid fever.

Acute splenic tumor is well marked in acute malaria, typhoid fever, typhus fever, relapsing fever, anthrax and pyogenic septicemia. It may be present in severe cases of variola, scarlet fever, inflammatory rheumatism, influenza, secondary syphilis, and other bacterial infections. It occurs in poisoning with potassium chlorate, phosphorus, pyrogallic acid, and other chemicals commonly recognized as blood poisons.

Jawein has emphasized the fact that the acute splenic tumor occurs in those infections and intoxications in which there is evidence of marked red blood-cell injury and destruction, and is not a feature of those diseases in which such injury does not take place. He attributes the increased size of the organ to the retention of the injured red-cells within the spleen and to the hyperplasia of splenic phagocytes called into function to dispose of these cells. Postmortem observations and laboratory experiments seem to confirm this point of view.

The acutely enlarged spleen seldom gives disturbing symptoms. It is of considerable clinical importance, however, due not only to the fact that its presence may be of diagnostic value, but also to the fact that the organ may rupture spontaneously or as the result of slight trauma. (*See* Rupture of Spleen.)

Chronic Splenic Tumors

A uniformly-enlarged, firm, splenic tumor is of frequent clinical occurrence. This condition may be so extreme as to merit the appellation "splenomegaly." Osler has classified the conditions under which such chronic tumors may be found as follows:

(1) Children: disturbances of metabolism and chronic intestinal infections, rickets, amyloid disease, and in a large but ill-defined group of intestinal disorders, particularly in the tropics; the pseudoleukemia infantum.

(2) In the infections: syphilis, malaria, kala-azar and other forms of tropical splenomegaly; Hodgkin's disease and tuberculosis.

(3) In primary disorders of the blood-forming organs: leukemia, pernicious anemia, chlorosis, hemochromatosis, polycythemic splenomegaly.

(4) In cirrhosis of the liver: syphilitic, alcoholic, hypertrophic of Hanot.

(5) Hereditary and family forms of splenomegaly: (*a*) with the congenital acholuric icterus; (*b*) with constitutional disturbances, dwarfing, etc.

(6) New growths and parasites: sarcoma, primitive epithelioma of Gaucher, echinococcus and the schistosoma of Japan.

(7) Splenomegaly not correlated with any of the above or with any known cause: Banti's disease with its three stages of (*a*) simple enlargement, (*b*) splenomegaly with anemia, (*c*) splenomegaly with anemia, jaundice and ascites.

In but relatively few of these conditions can the splenic lesion be considered as of primary importance. In the majority, the enlargement is a secondary phenomenon, and plays but little part in the symptomatology or clinical course of the disease of which it is a part. Its weight may cause a dragging pain localized in the splenic lesion or may lead to dislocation of the organ (*see* Wandering Spleen). Its size may cause pressure symptoms in neighboring organs. Chief among these are constipation from pressure on the colon, and gastric hemorrhage due to interference with the return of blood from the fundus. In rare cases, pressure upon the kidney has been found to result in hematuria.

The largest spleens are found in chronic myelocytic (splenomyelogenous) leukemia, splenomegaly of Banti type, splenomegaly of the Gaucher type, kala-azar and in some of the cystic conditions.

Splenomegaly of the Banti Type

Banti has described a disease in which, with marked enlargement of the spleen, there is a progressive anemia and eventually a cirrhosis of the liver with ascites. This is now commonly spoken of as Banti's disease. It seems safe to assume with Osler that Banti's disease represents but the terminal stage of a disease, the first stage of which is manifested by marked splenic enlargement (idiopathic or primitive splenomegaly), the second by splenomegaly and anemia (splenic anemia), and the last by the features described by Banti. A uniform pathological picture in the spleen in the various stages supports Osler's contention, which was based on clinical observation.

Etiology.—The disease is more common in males and most often begins before the middle period of life. The patients' histories give no evidence that malaria, syphilis or any infectious disease or that any chronic intoxication plays an etiological part. Banti early thought that the malady was a splenic form of Hodgkin's disease. Yates, Bunting and Kristjanson have isolated in pure culture from the spleen, in 3 cases, a diphtheroid organism resembling that repeatedly isolated from the lymph-glands in Hodgkin's disease. This finding has since been extended to a fourth case, with negative findings in a Gaucher spleen and in numerous spleens removed from cases of pernicious anemia. The etiological relationship of the organism has not been established. However, the occurrence of cirrhosis of the liver in late phases of Hodgkin's disease, the occurrence of alternate periods of progression and remission of periodic febrile periods and of progressive anemia in both diseases, with the pathological evidence that a fine diffuse fibrosis characterizes the lesions in both diseases are suggestive of a relationship between the two.

Symptomatology.—The enlarged spleen may be present for years without other symptoms being apparent than those attributable to its size. The only alarming symptom may be recurrent hematemesis. The amount of blood vomited may be large. With progressive enlargement of the spleen, there may develop a moderate anemia of a chlorotic type. The anemic period may last for years, 3 to 5 usually (Banti), at times from 10 to 12 (Osler). During this stage there may be periodic fever and slight albuminuria. Following the anemic stage Banti describes a transition period, in which there is, in addition to the splenomegaly and anemia, slight jaundice and diminished urine showing traces of bile. In the last stage there is diminution in size of the liver, with more marked jaundice, ascites, and commonly an afternoon febrile reaction.

Physical Findings.—The spleen is uniformly enlarged. In fact, there are no diseases except leukemia and Gaucher's disease which show regularly as large spleens. The organ may extend across the midline and into the right iliac fossa. It is firm, with smooth surface, and with the notches usually easily made out. Its position is superficial. In the later stages, there is diminution in the liver dullness. Jaundice may be well marked. There may be found edema of the extremities secondary to the anemia.

Laboratory Findings.—There is usually a moderate chlorotic anemia. The average red-cell count of Osler's 41 cases was 3,425,000 cells per cu. mm. with a color index of 0.5. Nucleated red-cells are often found in blood smears. The leukocytes are usually subnormal in number and averaged 4,520 in 14 of Osler's cases. It is usually said that the differential picture shows nothing characteristic. The author has found the same differential leukocyte picture as is seen in the early stage of Hodgkin's disease. The blood-platelets are increased in number. Albuminuria is a frequent finding in the disease.

Diagnosis.—Not all enlarged spleens associated with anemia are of the Banti type, and the diagnosis of this type except in its final stages may be difficult. The history and physical findings in the late stage should lead readily to a proper diagnosis. In diagnosis of the preascitic stage of Banti's disease, the leukemic spleen is easily eliminated from consideration by the blood-picture. The author has seen, however, a leukemic spleen removed as a Banti's spleen, owing to a failure to interpret properly the blood-picture during a relatively aleukemic period. The rarer condition of Gaucher's splenomegaly gives as a rule a longer history. The enlargement begins earlier and progresses more slowly. There may also be a history of family tendency to the disease. The patients show in addition a peculiar grayish or brownish pigmentation of the skin. The enlargement of the spleen with Hanot's cirrhosis of the liver is seldom as marked as that in Banti's disease, and in this condition the large, firm, hypertrophic liver, with symptoms referable to the liver, should serve to eliminate it from consideration. The history and the laboratory determination of increased fragility of the red blood-cells may serve to eliminate the splenomegaly of acholuric jaundice. In the experience of the author, although in Hodgkin's disease there may be a marked involvement of the spleen, it occurs in association with lymph-gland enlargement. This last is lacking in Banti's disease. The history of the patient aided by laboratory investigation should exclude the chronic malarial spleen or "ague cake." The age incidence and the blood-picture should eliminate the spleen of pseudoleukemia infantum of von Jaksch. Associated findings and clinical symptoms should exclude tuberculosis. The spleen in pernicious anemia is seldom markedly enlarged, and in all ordinary cases the diagnosis from Banti's disease should be easily made by proper consideration of the blood-picture.

Complications.—Aside from hematemesis and digestive disturbances, which are so frequent as to be considered almost as symptoms of the malady, complications are not numerous. As a result of the anemia, cardiac weakness may develop, and with it passive congestion, and edema. Nephritis has been described.

Treatment.—The **removal of the spleen** has proved curative in the early stages of Banti's disease, while **medical treatment** has been without avail. The operative mortality at the Mayo Clinic in the early stage is less than 10 per cent. (Balfour). In the ascitic stage the mortality following operation is at least 25 per cent. Even then, however, in view of the invariably fatal outcome of the malady, splenectomy is to be given consideration, as those patients who survive the operation show an arrest of the disease.

Prognosis.—In the non-operative cases the malady progresses slowly to a fatal termination. The course may extend over many years. Death may result from intercurrent infection or from anemia and general weakness in which recurrent hemorrhages may play a part.

Pathology.—Examination of the enlarged spleen of the Banti type shows its increase in size to be due to a great increase in the pulp, which also shows a marked diffuse fibrosis. The venous spaces are not obliterated but often seem encroached upon by the pulp hyperplasia and have a stellate form. In other cases they are markedly dilated. The malpighian corpuscles may show no lesion in some parts of the organ, while in others they are completely replaced by a dense fibrous scar tissue which apparently begins about the arteriole. Calcification of this scar tissue may occur. Some of the corpuscles may show hyperplasia of cells of the endothelial type. Infarcts are commonly found in the enlarged spleen, and also a capsular inflammation resulting in adhesions. Calcification and stenosis of the splenic and portal veins have been reported by Banti, by Dock and Warthin, and by others. The liver, when involved, shows a cirrhosis of the Laennec type. There is no noticeable lesion in the lymph-glands. There is an extension of red-marrow in the bones.

Gaucher's Splenomegaly

Gaucher's splenomegaly (primitive epithelioma of the spleen) is treated on page 305.

Tropical Febrile Splenomegaly

Synonyms.—Leishmaniasis; kala-azar; Burdwan fever; dum-dum fever, etc.

Etiology.—The disease is endemic in India, and has appeared there in epidemic form in several localities. The greatest prevalence of the disease has been in Assam, where it has been a large factor in the mortality for over 40 years. Natives are chiefly subject to the disease, though Europeans are attacked. It is preëminently a disease of youth, 50 per cent. of the cases occurring before the twentieth year. Since the discovery of its cause and the differentiation of the disease from malarial cachexia, it has been found to prevail extensively in China, India, Ceylon, Arabia, and Egypt.

The ultimate cause of the disease is an animal parasite, the *Leishmania donovani*, which was described almost simultaneously by Leishman and Donovan in 1903. The parasite belongs among the flagellates. It has an oval body which measures approximately 2.5 by 3.5 micra in size, and possesses a trophonucleus and a rodlike kinetonucleus. When artificially cultivated it develops a flagellum. It was first cultivated by Rogers in 1904. Patton showed that the parasite will thrive in the Indian bedbug, *Cimex rotundatus*, and his investigations indicate that this bug is the agent of transmission of the disease.

Symptomatology.—The disease is characterized by a very persistent fever of an alternating remittent and intermittent type, rapidly leading to a cachectic condition, with great enlargement of the spleen, and later of the liver, and by extreme wasting. The disease may be initiated by a chill, which is followed by a high remittent fever. Early, according to Rogers, the temperature chart is characteristic, showing two or even three sharp rises during each day for a period of several days. When the malady is well established, the remittent fever is found during periods of exacerbation of symptoms, and with a fall of temperature to the low intermittent type of fever the patient's condition shows improvement. The spleen shows early and progressive enlargement. Its size becomes enormous. Later the liver becomes enlarged and may extend to the level of the umbilicus. With the progress of the disease, anemia develops, and with it, marked bodily wasting. Bleeding from the gums and the nose is common. Purpura also occurs. There may be transitory edema of the face and of the extremities. In late stages ascites may be found.

PHYSICAL FINDINGS.—The skin of the patients is described as having a peculiar dusky or earthy hue. Petechiæ may be noted. The patients afford in general a striking appearance, owing to the marked contrast between the wasted body and the abdominal distention caused by the splenic and hepatic enlargement. In 27 per cent. of Roger's cases the spleen was found to reach to the anterior superior spine of the ilium.

LABORATORY FINDINGS.—There is a well-marked anemia. The red-cells are usually between 2,000,000 and 3,000,000 per cu. mm. The leukocytes are subnormal in number and may be as few as from 500 to 1,000 per cu. mm. The differential leukocyte picture shows marked increase in the large mononuclear forms of cells. In a large percentage of cases, by prolonged search the Leishman-Donovan parasite may be found in the polymorphonuclear leukocytes of the circulating blood. The parasites in the peripheral circulation are, however, few in number. Splenic puncture, which is not justifiable in many cases owing to the danger of hemorrhage, also reveals the parasites. The urine often shows albumin, and casts may be present.

Diagnosis.—This disease was considered a type of malarial cachexia until the discovery of the parasite. Rogers considers the early fever diagnostic and emphasizes the diagnostic value of the extreme leukopenia. The finding of the parasites establishes the diagnosis beyond doubt.

Complications.—The disease may be complicated by the presence of other parasitic diseases commonly seen in the tropics, especially by malaria and dysentery, and the cachexia of the patients renders them particularly liable to intercurrent bacterial infections, which may prove fatal.

Treatment.—There is no specific treatment for the disease and no treatment thus far applied has been very successful. The prolonged administration of large daily doses of **quinin** Rogers believes to be the most effective treatment. In fact, he claims a reduction of mortality to 75 per cent. with the use of this drug. Manson advises the use of **atoxyl**, and claims cures by its administration. Removal of the patient to a different climate is reported as being beneficial.

Prognosis.—The disease may run a course of from a few months to several years, but is eventually fatal in from 96 to 98 per cent. of cases. Death is often due to secondary bacterial infections.

Pathology.—There is a widespread distribution of the parasitic cause of the disease within the body, chiefly within endothelial cells, but also free in the tissue spaces in some organs. The parasites appear especially numerous in the spleen, liver, mesenteric lymph-glands, bone-marrow, kidney, testes, intestinal mucosa, and in skin papules and ulcers.

The spleen is much enlarged, is firm and friable. The malpighian corpuscles may be atrophic. There is no definite sclerosis of the organ but a marked infiltration of the pulp and distention of the sinuses with red blood-cells and endothelial phagocytes. The latter contain the parasites, often in large numbers. Groups of parasites are also found free in the pulp spaces and in the sinuses. The liver is large and shows parenchymatous degeneration. It contains large numbers of parasites in the endothelial cells. Cirrhosis may be present.

Infantile Kala-azar

In 1905 Pianese found in the spleens of children in southern Italy, who were suffering from anemia with splenic enlargement, a parasite similar to the Leishman-Donovan body, if not identical with it. Nicolle subsequently named this parasite *Leishmania infantum,* in the belief that the two were different species. Apparently the majority of the investigators of the diseases now believe that the two are identical.

The disease has been shown to prevail extensively in the Mediterranean basin and to affect chiefly children in their early years. Cases have been described in infants of six months, but the usual age of onset is in the second or third year. Adults, however, are attacked. In the regions where the disease is prevalent, Nicolle has shown that the dogs are heavily infected with the parasites, and the flea, *Pulex serraticeps,* is considered the agent of transmission from dog to man.

The symptoms, course, and pathology of the disease do not differ materially from those of the Indian kala-azar.

Histoplasmosis

In 1906, Darling found in Panama, in the spleens of three patients who had suffered over a long period from symptoms similar to those of kala-azar, a somewhat similar parasite which he designated the *Histoplasma capsulatum.* The organism is small, round, or oval, and from 1 to 4 micra in diameter. It shows an irregular chromatin nucleus and is encapsulated. No kinetonucleus is found. In Darling's cases, the organisms were widely distributed throughout the body in the endothelial cells of capillaries and lymphatics and in the reticulo-endothelial cells. Large numbers of parasites were found in many cells. In one macrophage 300 were counted. Pathologically, the cases showed large spleens, which were due to distention of the pulp and sinuses by red blood-cells, and phagocytes containing the parasites. There were necroses in the liver and in one case a marked cirrhosis of the organ. The lungs and intestines showed pseudo-granulomata, in which the parasites were found in phagocytes as in the other lesions.

Cysts of the Spleen

Etiology.—The majority of cysts occur in mid-life, although they may be found at either extreme. There appears to be a slightly greater susceptibility in women. In the etiology of cysts, other than the neoplastic, malaria and syphilis appear to be of some etiological moment. The great factor, however, is trauma. Spleen cysts bear no relation to congenital cysts of kidney and liver.

Symptomatology.—The symptoms of cysts of the spleen are those arising from enlargement of the organ. The chief is pain, variable in character, at times sharp, at others of a dragging nature, localized in the splenic region. Pressure symptoms noticeable in the stomach or intestine (commonly constipation, rarely diarrhea) may be present. With adhesions to the diaphragm, respiratory or cardiac symptoms may develop. Fever is not present except with secondary infection. Loss of weight and strength may develop with large cysts. Presence of the tumor may be the first symptom noted by the patient.

PHYSICAL FINDINGS.—The enlarged spleen is usually felt to the left of the mid-line, but may be dislocated to any part of the abdominal cavity. The surface of the tumor may be smooth, or irregular and nodular. It may be lobulated. Fluctuation may be present or the tumor may be firm.

Diagnosis.—Cysts of the spleen are seldom diagnosed before the abdomen is opened. There may be a clinical diagnosis of hypertrophy of the spleen, or, if the tumor is dislocated, it may be diagnosed as hydronephrosis, floating kidney or ovarian cyst. Puncture for diagnostic purposes is not justifiable.

Complications.—Cysts of parasitic origin are liable to bacterial infection and abscess formation, with or without extension to the peritoneum. With dislocation of the cystic spleen torsion of the pedicle may occur, giving rise to acute symptoms requiring operative intervention. Adhesions to surrounding viscera may lead to complications, such as intestinal obstruction.

Treatment.—The treatment is surgical. The exact procedure is determined by the conditions found upon opening the abdomen. When possible, **splenectomy** is the operation of choice. If adhesions prevent this, **incision and drainage** may be employed, though healing in these cases is slow. **Excision of the cyst** itself is often possible.

Prognosis.—In non-operative cases prognosis is difficult, as the condition is almost never diagnosed except at the operating table or at the postmortem table. Fowler has collected 27 cases treated by splenectomy with 24 recoveries, one death, and the result unstated in 2. Of 14 cases treated by incision and drainage, 7 recovered, 2 died and the result was not stated in 5.

Pathology.—Cysts of the spleen may be classified into parasitic and non-parasitic.

Parasitic cysts are in the main due to the cysticerci of the *Tænia echinococcus.* These cysts may be single or multiple, large or small. They show the usual outer connective tissue capsule (the host-reaction), with an inner laminated chitinous cyst-wall (parasitic) surrounding the membranous layer which gives rise to the scolices. Daughter cysts may be present. Healed, degenerated cysts may be found. The spleen may be the only organ affected or cysts may also be present in other organs. The spleen is affected in approximately 2 per cent. of the cases of echinococcus infection.

Non-parasitic cysts are classified as dermoid and simple cysts. But one dermoid cyst of the spleen has been described, that of Andral, reported in 1829. It contained hair and material of a sebaceous nature.

Simple cysts are of various characters. Fowler classifies them as follows:

(1) Traumatic cysts (hematomata, large and unilocular cysts, secondary serous cysts).
(2) Infoliation cysts (traumatic or inflammatory inclusions of peritoneum), small, multiple, superficial and deep.
(3) Dilatation cysts (ectasis of splenic sinuses).
(4) Disintegration cysts (of infarcted splenic tissue).
(5) Neoplastic types (hemangioma and lymphangioma).
(6) Degenerative cysts (arising from secondary changes in 5).

Of 65 cases of cystic spleens collected by Fowler, 43 had hemorrhagic and 22 serous contents. Hemorrhagic cysts may be so large as to contain several liters of blood, while one of the serous cysts is described as being as large as a football. The cysts may show a connective tissue capsule with or without endothelial lining. The infoliation cysts are usually small, multiple and close to the surface of the organ. Angiomatous and angiectatic cysts are multiple, often found throughout the organ, and give on section the picture of a multilocular cystoma.

New Growths

The spleen is seldom the seat of new growths of either a primary or a secondary nature. Among benign tumors, fibromata and lymph- and hemangiomata have been described in this location.

Primary cancer of the spleen has been reported several times, but as epithelium is not a normal constituent of the organ such reports must be received with doubt. This doubt is increased by the fact that 8 of 10 cases reported as cancer were without histological examination. The condition described by Gaucher as "primitive epithelioma," which is now designated as Gaucher's disease, is not epithelial in origin and is not a neoplasm.

Secondary cancer of the spleen does occur, although infrequently. In the author's experience, metastatic nodules from primary cancer of the breast have been most common.

Primary sarcoma of the spleen, though rare, does occur. Fibrosarcomata and small round-celled sarcomata have been reported. The author has reported as a sarcoma a diffuse tumor of the spleen pulp with metastases to liver, pancreas, gastrohepatic lymph-gland and subcutaneous tissue. Six similar cases were found in literature. These tumors are apparently derived from the cells of the reticulum and should probably therefore be classed as endotheliomata. Several tumor cases have been reported as lymphosarcomata. The relationship of this group to the endothelioma group, to the so-called benign endothelial hyperplasias, and to lymphosarcoma as commonly found in the intestine and mediastinum is not definitely established. In 1904 Jepson and Albert collected 32 cases of primary sarcoma of the spleen, including all types, and also those cases referred to above as having been reported as primary cancer. Council added 5 cases in 1912, giving a total of 37 cases.

The etiology of sarcoma of the spleen is as uncertain as that of sarcoma in other organs. Malaria and trauma have been reported as preexisting lesions in some cases.

The symptoms are indefinite. The presence of a splenic tumor, which is often nodular, is the most prominent. There may be a variable degree of pain.

Diagnosis is seldom made except at operation or in the postmortem room.

The treatment of the condition is splenectomy.

BIBLIOGRAPHY

Anatomy

MALL. Bucks' Reference handbook of the medical sciences, Vol. VII.
—— Am. Jour. Anat., 1902-3, ii, 315.

Physiology

EPPINGER. Berlin klin. Wchnschr., 1913, l, 1509, 1572, 2409.
HOWELL. Textbook of physiology, 1907, p. 759.
OZAKI. Jour. Med. Research, 1917, xxxvi, 413.
ZOJA. Folia haematologica, 1910, Vol. X, 232.

Splenectomy

BALFOUR. Internat. Abstr. Surg., Jan., 1918.
JOHNSTON. Ann. Surg., 1908, xlviii, 50.
KRUMBHAAR. New York Med. Jour., Feb. 6, 1915.
PEARCE AND ASSOCIATES. Jour. Exper. Med., 1912, xvi, 363, 375, 758, 769, 780; 1913, xviii, 487, 494, 665; 1914, xx, 19, 108, 122; 1915, xx, 319, 675; 1916, xxiii, 87, 97.

Warthin. Contributions to medical research. Dedicated to Victor C. Vaughan, 1903.

Abnormalities of Size and Shape

Albrecht. Ziegler's Beiträge, 1896, xx, 513.
Calvert. Am. Jour. of Med. Sc., 1905, cxxx, 311.
Hodenpyl. Med. Rec., New York, 1898, liv, 695.
Rokitansky. Pathological Anatomy, Vol. II, p. 130.
Sternberg. Virchow's Arch. f. path. Anat., 1903, clxxiii, 571.

Acquired Displacement

McDonald and Mackay. Lancet, 1909, ii, 1917.
Johnston. Ann. Surg., 1908, xlviii, 50.

Wounds of the Spleen

Berger. Archiv. f. klin. Chir., 1902, lxviii, 768.

Rupture of the Spleen

Berger. Archiv. f. klin. Chir., 1902, lxviii, 768.
Johnston. Ann. Surg., 1908, xlviii, 50.
Noland and Watson. Ann. Surg., 1913, lvii, 72.
Ross. Ann. Surg., 1908, xlviii, 60.
Simpson. Lancet, 1907, ii, 364.

Infarct of the Spleen

Karsner and Austin. Jour. Am. Med. Assn., 1911, lvii, 951.
Nuzum. Jour. Am. Med. Assn., 1918, lxx, 282.
Welch. Allbutts' System of medicine.

Abscess of the Spleen

Elting. Ann. Surg., 1915, lxii, 182.
Johnston. Ann. Surg., 1908, xlviii, 50.
Spear. Jour. Am. Med. Assn., 1903, xli, 304.

Tuberculosis of the Spleen

Winternitz. Arch. Int. Med., 1912, ix, 680.

Acute Splenic Tumor

Jawein. Virchow's Arch. f. path. Anat., 1900, clxi, 461.

Chronic Splenic Tumors

Osler. Brit. Med. Jour., 1908, ii, 1151.

Splenomegaly of Banti Type

Balfour. Internat. Abstr. Surg., 1918, 1.
Banti. Ziegler's Beiträge, 1898, xxiv, 21.
Dock and Warthin. Tr. Assn. Am. Phys., 1903, xvi, 522.
Osler. Brit. Med. Jour., 1908, ii, 1151.
Yates, Bunting and Kristjanson. Jour. Am. Med. Assn., 1914, lxiii, 2225.

Tropical Febrile Splenomegaly

Donovan. Brit. Med. Jour., 1903, ii, 79.
Leishman. Brit. Med. Jour., 1903, ii, 1252.

Leishman. Brit. Med. Jour., 1904, ii, 642.
Patton. Brit. Med. Jour., 1907, ii, 78.
——— Brit. Med. Jour., 1912, ii, 1194.
Rogers. Brit. Med. Jour., 1907, i, 427, 490, 557.

Infantile Kala-azar

Jemma and Di Cristina. Centralbl. f. Bakteriol., 1911, lix, 109.

Histoplasmosis

Darling. Jour. Am. Med. Assn., 1906, xlvi, 1283.
——— Arch. Int. Med., 1908, xi, 107.
——— Jour. Exper. Med., 1909, xi, 515.

Cysts of the Spleen

Fowler. Ann. Surg., 1913, lvii, 658.

New Growths

Bunting. Univ. Pennsylvania Med. Bull., 1903, 318.
Council. Ann. Surg., 1912, lvi, 915.
Jepson and Albert. Ann. Surg., 1904, xl, 80.

CHAPTER IV

GAUCHER'S DISEASE

BY N. E. BRILL, M.D., AND F. S. MANDLEBAUM, M.D.

Introduction, p. 305—Definition, p. 306—Etiology, p. 306:—Predisposing causes, p. 306—Symptomatology, p. 307:—Mode of onset, p. 307; Objective symptoms, p. 307:—Absence of jaundice and ascites, p. 312—Subjective and occasional symptoms, p. 312—Diagnosis, p. 313—Complications, p. 317—Treatment, p. 317—Prognosis, p. 318—Pathology, p. 318:—Pathological conditions simulating Gaucher's disease, p. 328—Historical summary, p. 328—Bibliography, p. 335.

Introduction.—While enlargements of the spleen were well known before the nineteenth century, no attempt at differentiating them had been made until Bennett in England and Virchow in Germany almost simultaneously described one type in which an enlarged spleen was associated with changes in the white blood-cells. This discovery removed the leukemias permanently as an entity from the general group. Investigations on the part of others subsequently succeeded in separating another class of splenic enlargements, a class in which a distinct differentiation seemed to be established by marked changes in the erythroblastic elements of the blood, and which seemed to be the essential pathologic feature which defined the class of grave or pernicious anemia. Even before the discovery of the latter group, it was known that the granulomata, particularly tuberculosis, syphilis, and Hodgkin's disease, produced enlarged spleens, in some instances, and that a similar splenomegaly attended some cases of chronic malarial fever. Nevertheless there still remained a large undifferentiated group of cases of splenomegaly, some of which were associated with anemia, with hemorrhagic tendencies, with jaundice and ascites. These puzzled the clinician and were jumbled into a motley class to which the name of splenic anemia was given. The last may in the future admit of still further differentiation. Of recent years it was seen that a disease with distinctive clinical and pathological features had been concealed in the large group of splenic anemia. Through the efforts of Brill this disease at last achieved individualization, and it was then termed by the authors Gaucher's disease, by which name it is now generally known. Even though Gaucher's disease has a definite clinical picture and a distinctive, characteristic, and unique pathological histology, it is difficult to place it in its proper category in medical nosology. It might be classified among the diseases of the hematopoietic system, since, even though its nature is as yet unknown, it is accompanied by a cellular development of a distinctive type which involves the bone-marrow, the spleen, the lymph-nodes, and the liver. Gaucher was the first to describe the pathology of the spleen in this disease, not knowing that he was dealing with an hitherto unrecognized and undescribed affection, but presented the findings in his case as those of a primary epithelioma of the spleen. Because he was the first to describe the peculiar cells which are characteristic of this, and which are found in no other disease, the authors have insisted upon giving the disease the name of that renowned French dermatologist. Its description is given a special place in this volume because it does not belong specifically to the diseases of the spleen, any more than it does to diseases of the bone-marrow, or to those of the liver or even of the lymph-nodes.

Definition.—Gaucher's disease is one of infancy or early childhood, and commonly affects many members of one generation of a family, though it has no hereditary features. It is characterized by a progressively increasing enlargement of the spleen, which often reaches colossal size, by a similar though later enlargement of the liver, by a brownish discoloration or pigmentation of the skin, chiefly of the face, neck and hands, by peculiar changes in the ocular conjunctivæ, giving rise to cuneiform thickenings extending from the corneal margins to the inner and outer canthi. It is later accompanied by an anemia of the chlorotic type. Hemorrhages occur frequently from the mucous surfaces, and occasionally in the skin. The blood, even in the early stages, shows a persistent leukopenia, which attends the disease throughout its entire course; the erythrocytes, however, are not altered in shape, size or number, nor is there a hemoglobinemia, until the disease has lasted a few years. Even then the anemia does not become very pronounced. The disease is a particularly chronic one, often of many years' duration, and it does not materially disturb the health or physical activities of the afflicted individuals. Jaundice is not present and ascites is a very rare accompaniment. It has none of the characters of malignancy, though the patients become at times very emaciated; they usually die of some intercurrent affection.

The characteristic pathological feature of this disease is the presence of numerous, large, unique cells which are confined to the spleen, liver, lymph-nodes and bone-marrow; they occasion the enlargement of the spleen, liver and of the abdominal and mediastinal lymph-nodes, though the superficial lymph-nodes are usually not enlarged. These distinctive cells are found in no other disease. In instances in which the disease is not recent, all these organs contain pigment which gives the iron reaction. It is the authors' belief that the disease is due to a metabolic disturbance, creating an unknown toxic or irritant agent which directly affects the "reticulo-endothelial cells" of the hematopoietic system.

Etiology.—PREDISPOSING CAUSES.—*Age.*—We have said that this is a disease of early life. This is true for the most part; it is even a question whether all of the cases do not start in infancy or childhood. In the larger majority of the cases reported in literature, the disease was discovered before the age of 12 years; it began in infancy and before the age of 5 in several instances (8 cases). It is because of its insidious onset and development, and the absence of discomfort and complaints, that the disease does not obtain recognition in its early stage.

Sex.—By far the greater number afflicted with this disease are females, males furnishing only 7 out of 23 cases reported in literature.

Familial Occurrence.—A noteworthy feature is the presence of this disease in more than one member of the same generation of the family. It is not transmitted by either parent; several children of parents who have had the disease have been seen to be free from it. The authors have under observation the son of an affected father who died of the disease who is now 19 years old and is free from it, and in another family two daughters, aged respectively 27 and 25 years, whose mother has had the disease for at least thirty years, and in both of whom it is absent. The familial occurrence has been noted in almost half of the reported cases.

Symptomatology.—MODE OF ONSET.—This is a disease accompanied by signs, rarely by symptoms. Not infrequently the mother or nurse, in undressing the young child, or a physician who is making a physical examination of the patient, notices that the abdomen is enlarged laterally to the left. It is the *enlargement of the abdomen,* or a physical examination of the abdomen, that usually reveals the existence of this disease to the physician, in the course of an inquiry as to the presence of some other disease, so insidiously does it develop. Where such an examination has not been made, or where the parent or nurse has been particularly unobservant, this progressive, slow enlargement of the abdomen may not be discovered until the spleen has reached such a large size that it gives rise to a dragging sensation in the side, when the patient himself makes the discovery, usually as late as adolescent life, and sometimes not until adult life is reached. When the patient is brought to the physician, the latter, in the course of the examination, discovers that the *liver is also enlarged,* that the patient is *pale,* that his skin, particularly that of the face and neck, is the seat of a *discoloration* of a yellowish or yellowish-brown hue, not unlike the tan which covers the face of people who live in the tropics. Inquiry reveals that the patient has been growing thinner, that he has had attacks of *nose-bleed* rather frequently, and that sometimes, rarely, it is true, there may have been a *hematemesis,* or even an attack in which the patient noticed some *tarry, blood-like stools.* More frequently the patient will say that if he suffered a slight bruise, it left a large black and blue mark on the skin; or, in fact, he may spontaneously confess to having frequently noticed the presence of *ecchymoses* in the skin not due to any injury of which he was aware.

OBJECTIVE SYMPTOMS.—*Shape of Body.*—After the disease has existed for some time the shape of the individual becomes rather characteristic, owing to the simultaneous enlargement of liver and spleen. The thorax and abdomen enlarge in such a way as to give to the body a *barrel shape,* the largest diameter being over the 5th, 6th and 7th ribs, tapering above toward the neck and below toward the pelvis; this shape, together with the emaciated arms and legs, gives the patient a very unusual and striking appearance.

The enlargement is not as a rule accompanied by pain, nor does it interfere to a great extent with the patient's activities, even when pronounced. In two instances the patients were able to swim, play tennis, and attend to their business occupations with undiminished vigor. One of these, now 50 years of age, in whom the disease has been observed by the authors for over 30 years, has at present a spleen and liver which together occupy more than seven-eighths of her entire abdominal cavity. She complains occasionally only of dragging discomfort.

Conjunctival Changes.—When patients with this disease are examined more closely and in a good light, almost all will show a peculiar change in their ocular conjunctivæ. On either side of the cornea of both eyes, a yellow, wedge-shaped, thickened elevation may be seen, usually from 1 to 2 mm. high, and extending from the corneal margins symmetrically to the inner and outer canthi, the base being at the corneal margin and the apex toward the canthus. When it is fully developed, the length of the wedge is often from 5 to 7 mm., with a base of from 3 to 5 mm. These dimensions, however, are only attained in cases of long duration. In the early stages of the disease these thickenings, unless searched for in a good light, may escape observation, owing to their small size. As a rule they develop first on the nasal side at the corneal margin, and later the temporal side of the cornea becomes involved. Their development and growth are very slow. Their color becomes more ocher-like as they enlarge, being at first a pale yellow, and they glisten by reflected light. They are almost invariably present; their presence is to be regarded as of great diagnostic value. In some respects they resemble the lesion of the conjunctivæ known as pinguecula.

Enlargement of the Spleen.—This is a very important feature of the disease. The spleen grows slowly and progressively and only terminates its growth with the death of the patient. The distortion of the thorax and abdomen induced by its growth is in direct proportion to the increase in the size of the spleen and the liver, the latter, however, never reaching the size of the former. At first the abdomen and thorax are asymmetrical, the left side being the larger and not infrequently showing a well-marked protrusion. With the subsequent enlargement of the liver, the right side increases in size, giving a more symmetrical appearance to the protruding trunk, producing the barrel-shaped contours to which we have already referred.

The spleen after many years reaches colossal proportions; it attains dimensions larger than in any other disease, not even excepting myeloid leukemia. It can be distinctly and readily felt through the thin abdominal walls, and its posterior border can be palpated in the left loin; its lower border often extends below the iliac crest into the pelvis, where it becomes lost to the palpating finger. Palpation of the anterior border reveals a dull, rounded edge, not a sharp one, and the presence of one, two or three distinct notches, sometimes wide enough to admit two fingers; this border when it reaches the umbilicus not uncommonly bends suddenly in a convex curve across the right side of the abdomen, at times extending halfway over the right abdominal sector toward the right iliac spine, when it bends again to the left, to dip down into the pelvis on the left side. When the spleen is as large as this, it covers the enlarged liver, lying over a part of its upper surface. The surface of the spleen is felt as a rule to be smooth; rarely can tuberosities or irregularities on the surface be mapped out by the touch. By percussion, the upper border of the splenic dullness in the left axillary line may be determined to exist even as high as the fifth rib.

Enlargement of the Liver.—This condition follows at a later date than enlargement of the spleen. The liver may reach very large dimensions, though never as large as those of the spleen. The enlargement is likewise slow and progressive; many years elapse before the liver reaches its larger size. When very large it has been found on percussion to reach as high in the thorax as the third interspace; its lower border has been felt posteriorly and in the axillary line just above the crest of the ilium; this border in front is concealed by the enlarged spleen which usually covers it; it is sharper than the border of the spleen. The surface of the liver is uniformly smooth. In one of the authors' cases, the combined weight of the liver and spleen exceeded one-fourth of the entire body weight.

Skin Condition.—A peculiar discoloration or pigmentation of the skin accompanies the disease, not manifest in the very early stages, but appearing soon thereafter. It is called by most writers a pigmentation, though it is confined only to the skin of those parts of the body which are exposed to the light, namely to the face and neck, wrists and hands. In one case pigmentation of the abdomen was noted. The discoloration is uniform in distribution and in density, and is not collected in patches; it resembles very closely in character the skin of those who live for years in the tropics, assuming a light yellowish-brown or ocher tone. The color becomes uniformly darker as the disease advances. Occasionally the skin is darker over the nasal bones and about the eyes than on the rest of the face; this region may become the seat of an erythematous patch, which infrequently has a butterfly shape and is reddish-brown in color.

Hemorrhages commonly occur in the skin and modify the nature of the discoloration to the extent that the hemorrhagic areas show patchy spots of almost black pigmentation. These are most frequently found in the skin covering both tibiæ and, less frequently, the forearms and arms.

Occasionally hemorrhagic furuncles develop, which usually break down, leaving, for the time being, ulcerated surfaces which slowly heal. These are usually to be found on the thighs, legs and forearms. After healing is complete, the areas involved show a still deeper black pigmentation. Thus, at times, a patient may present a slight yellowish-brown discoloration of the face and hands; on exposure of the legs, which are the usual site of these furuncles, large, black, permanently pigmented spots become revealed. In the majority of cases, however, the pigmentation is not a very marked feature, and it may require special observation under favorable conditions of daylight to demonstrate it. In fact, daylight, rather than artificial light, should be preferred in making observations of the skin and conjunctivæ.

A tendency to ecchymoses exists even early in the course of the disease and the skin will not infrequently show, over scattered areas of the thighs and legs, forearms and arms, "black and blue" marks, because these parts of the body are most subject to trauma. The slightest bruise may produce such an ecchymosis. Small petechiæ, varying in size from that of a pin head to that of a lentil, are found occasionally.

Most of the patients with this disease perspire very profusely, even in winter. Occasionally this excessive sweating gives rise to miliaria and sudamina, which are usually found on the skin of the forehead, nose and trunk; these sudamina may become hemorrhagic.

The peculiar brownish-yellow discoloration of the skin and the subicteric hue of the ocular conjunctivæ have induced some writers to regard these as signs of jaundice. Jaundice as such, in the authors' opinion, is not present in this disease. Their examinations and analyses of blood and urine show a total absence of bile, though urobilin is increased in both.

Hemorrhages.—The tissues from which bleeding usually occurs are the mucous membranes. It is common from the nose, and almost as frequent from the gums, which, as the disease advances, are usually swollen and spongy. Hemorrhages from the bowel with tarry stools occur but are not so common. The authors observed hematemesis in 2 cases, although the stomach is by far the rarest site for hemorrhage to take place. The hemorrhages are rarely profuse in amount or of long duration, for the coagulation time of the blood is not delayed. Epistaxis may recur every week or two, and the bleeding from the gums starts with almost every trauma. They are most prominent when the disease has existed for some years, and furnish an important factor in the production of the anemia which is a late accompaniment.

Hemorrhages into the skin occur as ecchymoses, purpuric spots and petechiæ, of which ecchymoses are the most common. One patient who died of this disease had a bloody effusion in the pleural sac as well as a hemorrhagic pericardial effusion.

Blood Changes.—A marked diminution in the number of white blood-cells occurs even very early in the disease. The leukopenia is a definite and permanent accompaniment; it is almost invariably present and lasts as long as the disease. While the average number of leukocytes per cu mm. has been determined to be 4,600, variations in number occur between a minimum, as observed in one case of 500 per cu. mm., and a maximum of 13,000. It is rare to find a higher white blood-count than 5,000 per cu.mm.; the common average is considerably lower, most of the cases showing about 3,500 per cu.mm.

The proportions of the various leukoblastic elements of the blood show no demonstrable change from the normal; the average differential count is as follows: polynuclear cells, 66 per cent.; small lymphocytes, 20 per cent.; large lymphocytes, 13 per cent.; eosinophils, 1 per cent. This count is based on the average deduced from the counts recorded in all the observed authentic cases of the disease.

In two cases mast-cells have been found to the extent of 0.8 per cent. and 0.5 per cent., respectively. Their presence has no diagnostic significance. Even the red blood-cells are not reduced to any extent until long in the course of the disease, the red cell-count being for quite a long time very close to that of blood from a normal individual. As the disease progresses, a slow diminution in the number of red blood-cells becomes apparent. The hemoglobin content of the red blood-cells suffers relatively in diminution much more than the number of the cells; even while the number of red-cells is close to normal, the hemoglobin may be but 75 per cent., giving the blood-picture of a chlorotic type of anemia; in other words, an anemia with a low color index exists. This hemoglobinemia is not discoverable at this stage by any definite pallor of the skin of the mucous membranes of the lips, gums or palate. The average amount of hemoglobin as estimated from all the recorded cases is 65 per cent., the minimum recorded being 35 per cent., and the maximum 92 per cent. When the disease is well advanced, the average number of red blood-cells, estimated by the authors from all the reported counts, is 3,700,000 per cu.mm. One writer reports a case with a hyperglobulism, namely, 6,000,000 per cu.mm. Thus it may be inferred that an anemia, due to a diminution in the number of red blood-cells, is not a feature of this disease.

The morphology of the red-cell is also not much affected, the cells retaining their normal contour and size, the color of the cell, however, being a little paler. Nucleated red-cells are under ordinary conditions not found; in only 2 cases have normoblasts been observed, and then only one cell in each of these cases was revealed during the blood examination; megaloblasts have been noted once; polychromasia and basophilic stippling occur very rarely. It is really noteworthy that a disease which so completely involves the entire hematopoietic system in its pathological process should be lacking in demonstrable changes in the morphological characters of the blood. It should be remembered that the pathological element existing in the hematopoietic organs in Gaucher's disease, the large characteristic cell, has never been found in the peripheral blood, doubtless because its size (40 to 100 microns) is too large to allow of its admission into the skin capillaries.

It has been shown that the cholesterin content of the blood in many affections of the spleen or liver, especially in cases accompanied by non-obstructive icterus, such as Banti's disease, pernicious anemia and some forms of splenomegaly with blood changes, is either normal in amount, or, in many instances, decidedly less than normal. Such is the case in Gaucher's disease. After splenectomy for Gaucher's disease, the cholesterin content of the blood is always elevated for a certain length of time but returns slowly to normal.

Lymph-nodes.—As a rule, the superficial lymph-nodes of the body are not enlarged. Occasionally there will be found, particularly in the axilla, and in the groin, small, fairly firm, quite movable, solitary lymph-nodes about the size of a lentil or pea; careful search, however, must even be made to discover these, as they easily elude the palpating finger, owing to their great movability. This is in apparently strange contrast to the fact that the deep abdominal and thoracic lymph-nodes are always found on autopsy to be greatly enlarged.

Emaciation.—In the patients in whom the disease is well advanced there is a decided loss in the adipose tissues. The loss in subcutaneous fat is general in its distribution, the arms and legs being very thin, and the neck scrawny; these features, associated with the very protuberant abdomen and lower thorax, and the pigmentation of the skin, give a somewhat characteristic and individual appearance to these patients.

Absence of Jaundice and Ascites.—Inasmuch as the presence of jaundice and ascites has an important bearing on the determination of the form of splenic anemia to which Banti has attributed specific characters, it should be remembered that these symptoms are absent in this disease. The brownish-yellow discoloration of the skin, to which we have referred, is limited to the parts of the body which are exposed to light, thus differing from a jaundiced skin in which a general distribution of the color over the entire skin surface is the characteristic feature. It is true, some writers have spoken of the discoloration of this disease as jaundice, though incorrectly, because bile-pigment has not been found in the blood or urine. Ascites is almost invariably absent; in fact, only one case has been recorded in the literature.

SUBJECTIVE AND OCCASIONAL SYMPTOMS.—We have alluded to the fact that this disease is one chiefly associated with and determined by objective phenomena; occasionally the much enlarged liver and spleen give rise to a dragging sensation in the abdomen, at other times to a distinct pain, particularly occurring on the left side in the splenic region. The pain is at times complained of as being sharp in character and the patients remark that it comes and goes. It is not constant and it may not recur until after a month or more of absence. When present it may be explained by the development of local areas of perisplenitis which accompanies the pathological changes in the spleen. During the attacks of pain, tenderness may be elicited by pressure on the parts of the skin lying over the enlarged spleen; it is usually present during the acute stage of perisplenitis and disappears with the subsidence of this inflammatory condition; it likewise occurs paroxysmally, though in some cases tenderness may never be a feature of the disease.

Pain and tenderness over the liver are only exceptionally observed, notwithstanding the large size which this viscus may reach. It is really remarkable that so little discomfort, so little pain and tenderness should accompany this colossal enlargement of spleen and liver.

A few patients in the advanced stages of the disease have complained of pain in the long bones, especially at the lower ends of the femur and tibia. In these cases tenderness over the seat of the pain cannot be elicited. While the bone-marrow is involved greatly in this disease, bone tenderness, such as exists in pernicious anemia, is not present at any time in its course. At times these patients will complain of pain and tenderness in all the muscles of the thigh and particularly of the calf of the leg.

Diagnosis.—The recognition of this disease, in its earliest stages in the first member of a family to be affected, is practically impossible. Its existence may be suspected when more than one child of the same parents has a combined splenic and hepatic enlargement. Nevertheless, while there are no individual symptoms which are pathognomonic of this disease, we insist that a definite association of certain symptoms is sufficient to enable the physician to determine the presence of the disease in its later stages. In fact, when the disease has sufficiently developed so as to give rise to a distinctly large spleen, even though but one member of a family be affected, the diagnosis, while difficult, may possibly be made because of the association of the symptoms of large spleen, enlargement of liver, leukopenia, the conjunctival lesion, and because of the absence of anemia, of jaundice, of ascites and of changes in morphology of the red-cells and leukocytes of the blood.

Diagnosis is much more readily made in the advanced cases of the disease, when it should be fairly possible at all times. With the association of the objective criteria just mentioned, it should be remembered that the chronicity of the affection, its familial occurrence, the relative well-being and comfort of the patient—out of all proportion to the tremendous hepatomegaly and splenomegaly—the hemorrhagic tendency, manifested chiefly in epistaxis, bleeding gums and occasionally in hematemesis and melena, the ecchymoses in the skin, the occasional evidence of hemorrhagic furuncles, the pigmentation, the perspiration sometimes accompanied by sudamina, the ever-present leukopenia with the chlorotic anemia, and the absence of jaundice and ascites furnish the strongest corroborative evidence of the existence of this disease, and not of any other form of splenic anemia or so-called Banti's disease, with which this disease may most readily be confounded.

Differential Diagnosis.—The clinician should bear in mind all the similar conditions in which splenomegaly occurs and evaluate the same before reaching a definite judgment. The following are, in the order of their common prevalence, most likely to be confounded with Gaucher's disease: pernicious anemia, Hodgkin's disease, leukemia, Banti's disease and other forms of so-called splenic anemia, Hanot's disease, and chronic splenomegalic acholuric jaundice. Let us call attention in brief statements to the special differential symptom values of each of these as compared to the elements present in Gaucher's disease.

Pernicious Anemia.—In pernicious anemia the high color index, the marked diminution in number of the red blood-cells; their changes in contour and size, the macrocytosis and microcytosis, the polychromasia, the various forms of nucleated red-cells, the excessive and distinctive lemon-yellow pallor of the skin, the retention of the subcutaneous fat, are in themselves distinctly suggestive of the presence of pernicious anemia, even though a moderate splenomegaly accompanies this disease.

Hodgkin's Disease.—It does not seem likely that Hodgkin's disease would ever be confounded with Gaucher's disease if the ordinary form of the former in which pyrexial attacks, large swellings involving chiefly the superficial and deep lymph-nodes, were its only manifestation. Yet occasionally the spleen shows an enlargement in conjunction with the enlarged superficial lymph-nodes; in the latter event a mistake in diagnosis might possibly be made. If one remembers that no palpable enlargement of the superficial lymph-nodes occurs in Gaucher's disease, an error in its identification will be avoided. However, some clinicians agree that there is a splenomegalic form of Hodgkin's disease in which the enlargement of the superficial lymph-nodes may be entirely wanting: this form is not generally accepted. Even though it may exist, it is not associated with a tremendous enlargement of the liver, with the brownish-yellow discoloration of the skin, and the conjunctival changes which identify Gaucher's disease.

Leukemia.—Leukemia, whether myeloid or lymphoid, has characteristic changes in the leukocytes in each form and is accompanied by a diffused enlargement of the superficial lymph-nodes, less as a rule in the myeloid than in the lymphoid type. The blood-picture alone would identify the presence of a leukemia, except perhaps in the stage of remission of that disease, when the retention of a large spleen might be the only remnant of its symptomatology. The characteristic blood-picture of leukemia and the enlarged superficial lymph-nodes would turn the decision against the existence of Gaucher's disease. Even in the remission period of a leukemia, when the enlarged lymph-nodes and the leukocytosis may have disappeared, though a large spleen is retained, the condition can be determined to be one other than Gaucher's disease. However, the real condition may remain in doubt; for while, in the remission stage, leukemics do not show a leukopenia, very frequently their white blood-cells are present in inverse proportional distribution, the mononuclear white blood-cells exceeding, at times very largely, the polynuclears, which never occurs in Gaucher's disease. Usually the leukemic pallor remains in the remission, a pallor sufficiently distinctive to separate it from the yellowish-brown discoloration of the face present in Gaucher's disease.

Splenic Anemia and Banti's Disease.—It was among this motley group that Gaucher's disease was originally concealed. While they have many signs in common, differentiation of an advanced Gaucher from this group is not difficult. The features common to all are the splenic enlargement, the chronicity, the anemia of the chlorotic type, the tendency to hemorrhages from the mucous membranes, and the presence of a normal or diminished leukocytosis.

The clinical factors, which serve to differentiate Gaucher's disease and which enabled the writers to make the first diagnosis of this disease recorded in medical literature, are the following:

SPLENIC ANEMIA AND BANTI'S DISEASE	GAUCHER'S DISEASE
Chronicity: Of considerably shorter duration, relatively, twelve years being the maximum.	Longer duration with maximum of thirty-six years.
Color: Skin, pale — In so-called Banti's disease, absolutely uniformly jaundiced.	Skin only discolored over parts exposed to light; not jaundiced, but yellowish-brown pigmentation.
Anemia: Of early appearance and definitely pronounced.	Very late in appearance and only marked after many years.
Hemorrhages: More generalized, particularly common as hematemesis and melena.	Common from the gums and from the nose as epistaxis, rare as hematemesis and melena; hemorrhagic lesions of the skin more common than in splenic anemia; furuncles and sudamina often hemorrhagic.
Distress and feeling of illness.	Relative comfort and feeling of well-being.
Spleen: Enlarged moderately.	Colossal in size.
Liver: Enlarged slightly; and in Banti's disease supposed to be smaller than normal.	Much larger than in any form of splenic anemia and never decreased in size.
Conjunctivæ: Not the seat of any lesion.	Wedge-shaped thickening of yellow-brown color, similar to pingueculæ.
Sex: Disease is as common in males as in females.	Females show marked predilection to the disease; male sex definitely less affected, only 7 cases being reported as having occurred in males.
Ascites: Almost invariably present in Banti's disease.	Only one reported instance of ascites in the literature.
Consanguinity: No tendency to attack more than one child of a family.	Common tendency to appear as a familial disease in a single generation.

It was the utilization of these differential factors first pointed out by the writers which enabled other physicians, notably de Jong and van Heukelom, and also Reuben, to diagnose the presence of Gaucher's disease during life, which diagnosis was subsequently confirmed in each instance by histological examinations.

A method, which is not to be endorsed on account of its great danger, was used in two instances to settle the diagnosis between these conditions, namely, an aspiration puncture of the spleen through the abdominal wall with an exploring needle. Histological examination made of the cells resulting from such an aspiration would at once fix upon a correct diagnosis, because the characteristic cell of Gaucher's disease occurs in no other disease.

A search for the characteristic large cells in an excised superficial lymph-node has so far been unsuccessful. Further attempts should be made in a suspected case of Gaucher's disease, in the hope that a histological examination of the excised superficial node may establish the diagnosis.

Hanot's Disease.—While Hanot's disease is accompanied by both an hypertrophy of the liver and an enlarged spleen and is a disease which runs a chronic course, jaundice occurs early, is always present throughout, and pyrexial attacks attend its progress. The persistent jaundice, which occurs in varying degrees of intensity, may develop into an icterus gravis with a fatal cholemia at any time during its course. Leukocytosis is a usual concomitant. The spleen in this disease never reaches the size of that in Gaucher's disease. The jaundice, the pyrexial attacks, and the leukocytosis are likewise differential factors.

Other forms of enlargement of the liver associated with an enlargement of the spleen have been reported especially by French writers, who attempted to classify them, either in their relation to the time at which such enlargements occurred (*i.e.*, as to whether the hepatic enlargement preceded or followed the splenic enlargement, whether there was a presplenomegalic hypertrophic biliary cirrhosis, or a metasplenomegalic hypertrophic biliary cirrhosis) or in relation to whether the spleen or the liver was the larger, thus, hypersplenomegalic hypertrophic biliary cirrhosis. There are no definite data connected with any of the latter to warrant the formation of a special class; in fact, their clinical histories and pathological features are not sufficiently distinctive to justify specialization, and it is very likely that some of these may be examples of an unrecognized so-called Banti's disease or even of an unrecognized Gaucher's disease.

Chronic Splenomegalic Acholuric Jaundice.—This is a disease likewise often appearing in infancy and early childhood and also occurring in various members of a family, being frequently hereditary. It is accompanied by marked anemia, by considerable enlargement of the spleen and a lesser enlargement of the liver. It has, however, associated red blood changes, such as fragility of the red blood-cells, many normoblasts and megaloblasts at various times in its course (normoblastic and megaloblastic crises), and a considerable leukocytosis. These distinctive blood-changes would in themselves differentiate it from Gaucher's disease.

Complications.—These occur, if they occur at all, only late in the disease and are largely referable to the changes in the blood and blood-vessels which permit of an easy diapedesis of red blood-cells when complicating inflammatory processes develop; hence arises the frequency of the reported instances of *hemorrhagic pleural effusions,* and *hemorrhagic pericardial effusions. Thrombophlebitis* of the saphenous vein has been observed, as has been hemorrhagic colitis. *Furunculosis* is of relatively frequent occurrence.

A number of instances of *tuberculosis* have been reported as complicating this disease; in fact, it was at one time considered that the large cell process in the spleen in Gaucher's disease might have resulted from the influence of the tuberculous toxins, tuberculosis having been erroneously considered by some pathologists to be the attributable cause for the disease. It is needless here to discuss this relationship. Let it be understood that tuberculosis may develop in or precede the development of any disease. When it occurs in Gaucher's disease, it is as an entirely independent condition, and has no causal relationship with it.

Treatment.—When the pathogenesis of a disease is unknown, treatment for the most part must be based upon empiricism. At present, there is no agent which can be depended upon to arrest the disease. **Splenectomy** has been tried in a number of instances. Literature fails to disclose any communication as to the ultimate results of splenectomy in any of the instances in which the spleen was removed as a remedial agent for Gaucher's disease.

As this is a disease which lasts for many years, and one which in most instances does not produce much suffering, one should bear in mind, before suggesting splenectomy, that the operation is attended by an operative risk which is not inconsiderable. The writers fail to see how such a measure can control the course of a disease which is not confined to the spleen but which seems to invade almost simultaneously all the components of the hematopoietic system. To remove the disease it would be just as necessary to remove the lymph-nodes and the bone-marrow from the body as the spleen, which of course cannot be done.

Since the size and weight of the spleen produce symptoms which are the chief causes for complaint, measures looking toward their reductions have been employed; the agency which accomplishes these objects best has been exposure to the **x-ray.** There is no doubt that exposure of the splenic area to the *x*-ray will diminish the size of the spleen, but it does not arrest the disease or even retard the pathological process in the spleen; after such treatment is discontinued, the spleen becomes again enlarged. Exposure of the long bones to the *x*-ray has also been employed without apparent results. The skin of these patients is largely vulnerable to extensive *x*-ray treatment; burns are induced easily by the *x*-ray, hence care in its application must be observed. Deep pigmentation always results from the procedure.

The anemia which develops after the long continuation of the disease is best treated by the ordinary measures employed for the treatment of that blood disturbance. **Iron** and **arsenic,** the latter preferably by hypodermatic administration, seem to have the greatest influence in increasing the amount of hemoglobin. The tendency to hemorrhage is apparently lessened by the use of these agents.

A **well-regulated hygienic life** will insure to these patients for the most part considerable comfort and a very fair degree of well-being.

Prognosis.—DURATION AND TERMINATION.—The disease lasts for years and is essentially chronic. One patient reported by Schlagenhaufer lived for 36 years. One of the authors' patients is still living, having had the disease for over 30 years; they have also observed another case in which a splenectomy resulted fatally, after the disease had existed for 35 years. The average duration of all the authentic reported cases, in which death did not follow a splenectomy to which some had been subjected, was a little over fifteen years.

None of the patients observed by the authors or who have been reported in literature, except one, have died of the disease itself. All who died succumbed either to a splenectomy or to some other intercurrent or complicating factors. The causes of death in a few of the reported cases have been tuberculosis, pleurisy with effusion, pericarditis, and trauma. Operative removal of the spleen has been the cause of four deaths.

Pathology.—The distinctive feature of the disease is the presence in the spleen, liver, lymph-nodes and bone-marrow of peculiar, large cells with a characteristic type of cytoplasm. The average diameter of these cells is from 20 μ to 40 μ, but considerable variation in size occurs, so that cells three or four times as large as the average may be found. The cells are round or oval in shape, but occasionally they fuse together and form large syncytial masses or long strands. The nuclei are irregular in shape, small in size and eccentric in position. Two or more nuclei are frequently seen in a cell and occasionally as many as twenty may be found. Mitotic cells do not occur, but cell division by amitosis has been described. When the cells are stained with acid dyes a network of fine fibrils may be seen, running in a wavy, parallel course in the direction of the longitudinal axis of the cell, but when a cell has been cut transversely, the cytoplasm appears more or less stippled or granular. The cells frequently present elongated or irregularly shaped colorless spaces or vacuoles due to separation or crowding apart of the fibrils. Fat or lipoid substances have never been found in the large cells and microchemical tests as well as polariscopic examinations for these substances are always negative. Tests for glycogen, amyloid and oxydase are also negative. The action of potassium hydrate, hydrochloric acid or acetic acid has no effect on the cells. Alcohol, ether, chloroform, aceton and xylol bring out more clearly the fibrillar structure and produce a shrunken or wrinkled appearance of the cytoplasm. These reagents have no solvent effects on the peculiar substance in the cells, however, for there is no change in the staining qualities after their action. The nature of the substance is not revealed by chemical analysis of the spleen by simple extraction methods. The substance does not lie in the extractive group of lipoids, but may be of complex protein nature, probably in combination with lipoids. Attempts to break up this combination by the digestive action of pepsin and trypsin have been unsuccessful. When the disease has existed for quite a length of time pigment of a yellow or brownish color is found in some of the large cells. The pigment may occur in the form of crystals or as rounded masses, the latter usually giving a positive reaction for iron. The pigment is more abundant in the lymph-nodes than in the spleen or liver. There is no definite proof that the large cells possess properties of a phagocytic character.

The origin of the large cells has given rise to considerable controversy since the first description of the pathological histology of the disease. Some authors have stated that the cells arose from endothelium, others have described their origin from reticulum, while still others have claimed both sources. The recent investigations of Mandlebaum and Downey, however, have shown conclusively that the large cells have their origin in the reticular apparatus of the hematopoietic organs, though an additional origin from the endothelium of the venous sinuses in the spleen could not be denied.

SPLEEN.—This organ is always enlarged, but retains its normal shape and contour. The size and weight of the spleen depend upon the age of the patient and the duration of the disease. The largest recorded spleen measured 45 x 25 x 13 cm. and weighed 7,400 grams (nearly 15 pounds). The average weight in thirteen adults was 4,000 grams, and in six children 1,000 grams. The smallest spleen in a case occurring in childhood weighed 350 grams. The surface, as a rule, is smooth, but thickening of the capsule and areas of perisplenitis may be seen in cases of long duration. Occasionally, globular elevations are found on the surface, representing areas of hemorrhage which may then be seen on the cut surface of the organ. Localized depressions due to infarctions are not uncommon. The color is dark purple or brownish-red on the surface, but the freshly cut section is always reddish-brown or reddish-purple. The consistency is firm and the cut surface smooth, as a rule, though dotted with innumerable semi-translucent areas about one millimeter in diameter. Minute, hemorrhagic dots are not uncommon, producing a mottled appearance of the entire cut surface. Larger, rounded, hemorrhagic areas, one or more centimeters in diameter, or infarctions surrounded by hemorrhagic zones, are rather frequent. The hemorrhagic areas are often the seat of central necrosis. The Malpighian bodies are not visible, nor can the connective tissue framework be recognized. The vessels at the hilus are always large and greatly dilated, but their walls are normal. A cluster of enlarged lymph-nodes is usually present at the hilus and along the splenic vein. Smears made from the freshly-cut surface of the organ always show the characteristic large cells.

The microscopical picture is unique and characteristic. The pulp is nearly or entirely replaced by round, oval or irregularly shaped alveolar spaces containing the large cells. Many of the alveoli are lined by a single layer of these cells, others are completely filled (Fig. 1).

Some of these spaces are dilated venous sinuses, partially lined with flattened endothelial cells; others are simple alveolar spaces bounded by connective tissue septa devoid of endothelial lining. The adjoining sinuses frequently communicate with each other, or the wall may be broken and the sinus may communicate directly with the pulp. In addition to the large cells in the alveoli, numerous red blood-cells may be present, especially in the dilated venous sinuses (Fig. 2). Between the sinuses small collections of normal pulp cells are found, and scattered throughout the pulp numerous groups of large cells are encountered. Although some of the endothelial cells lining the sinuses may be swollen and vacuolated and in intimate contact with the large cells, there is no direct evidence that the latter originate from the endothelial cells. Nevertheless, some of the alveoli filled with large cells are bounded by an unbroken wall of connective tissue without an endo-

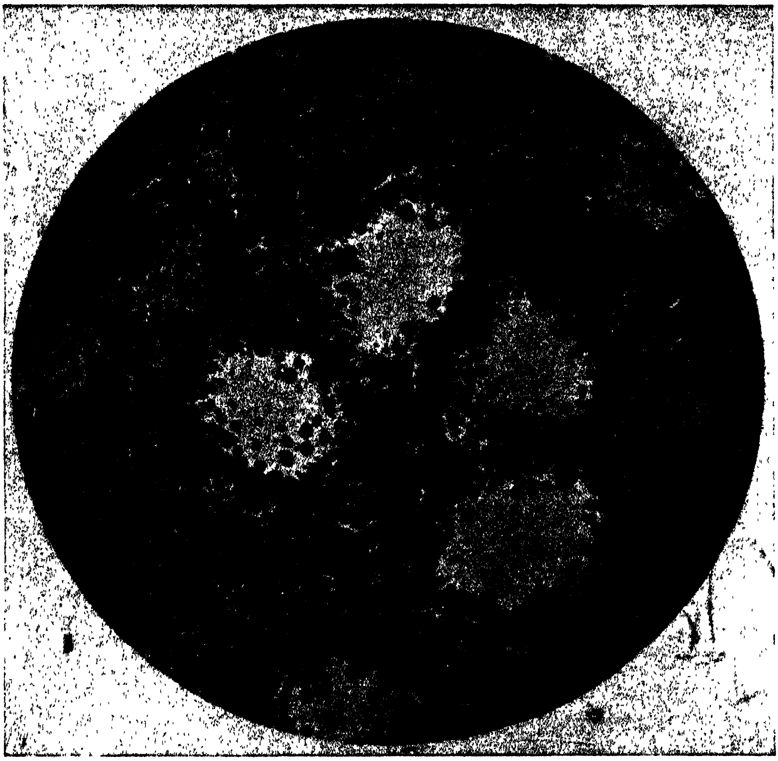


Fig. 1.—Microscopical Section of Spleen (Low Power).

In center of field dilated venous sinuses lined with large cells and distended with red blood-cells. Remainder of field shows alveolar spaces filled with large cells, also areas of normal pulp-cells, mainly at the periphery. X 70.

thelial lining, and this may be considered as indirect evidence for the view that the large cells are derived from the endothelium of the sinuses. In the lymph-nodes, positive evidence has been obtained that the large cells arise from the reticulum, and since direct communication exists in the spleen between many of the sinuses and the surrounding pulp, it is possible that a considerable number of the large cells in the sinuses are derived from the reticulum of the spleen and have come in from the surrounding pulp. The Malpighian bodies, in advanced cases, are usually few in number and normal in size, but in children they are frequently of enormous size. The germ centers are large, showing hypertrophy of the reticulum, an occasional Gaucher cell, fragmented lymphocytes, and marked phagocytic activity, as evidenced by the many Flemming bodies. Large cells are usually seen between the lymphoid cells at the peripheral portion of the follicles. In cases of long standing,

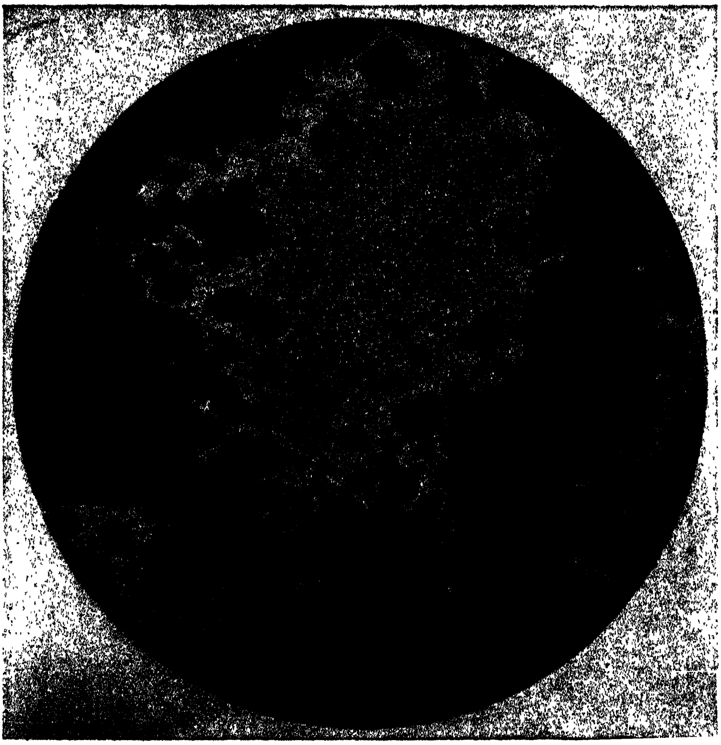


FIG. 2.—MICROSCOPICAL SECTION OF SPLEEN, CENTER OF SAME FIELD AS IN FIGURE 1 (High Power).

Note character of the connective tissue septa between adjacent sinuses. The red blood-cells are faintly visible. X 350.

areas of hemorrhage are common, also areas of degeneration, and pigment is always present. In addition to its presence in a limited number of the large cells, the pigment is found in the trabeculæ and in the walls of some of the capillaries. It is brown or brownish-yellow in color and a positive test for iron can be obtained.

Liver.—This organ is always enlarged, its size depending upon the duration of the disease and the age of the individual. The average weight in six adults was 3,200 grams, the largest weighing 4,800 grams (10 pounds), the smallest 2,040 grams. In children the surface is smooth and glistening and the color light yellowish-pink. The surface, in adults, may present some thickening of the capsule due to areas of perihepatitis, and the color may be described as grayish-brown or brownish-red. On section, the color is brownish-pink or red and the parenchyma, usually succulent, bulges above the line of the cut surface. The

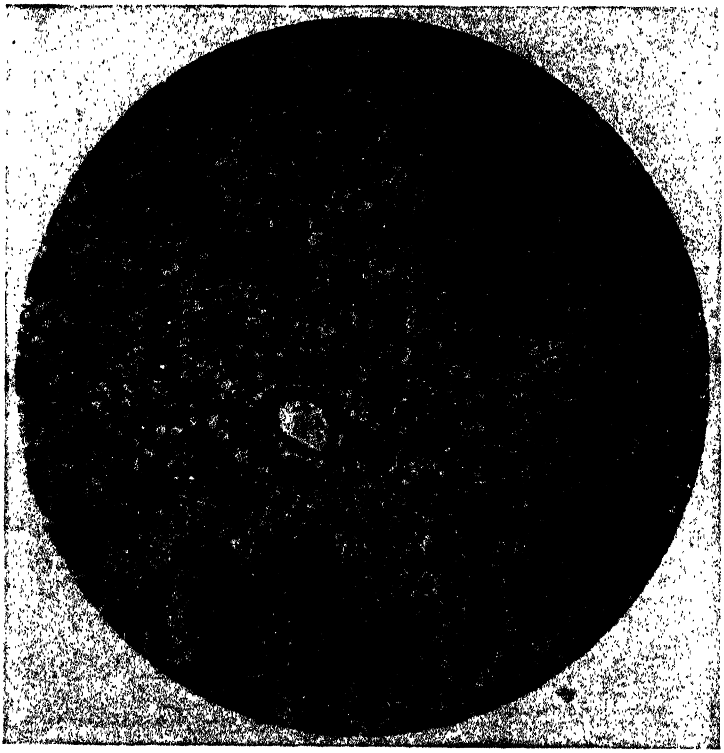


Fig. 3.—Microscopical Section of Liver (Low Power).

The increase in interlobular connective tissue is clearly seen, also the invasion into the lobules. The individual large cells are not distinctly visible with this magnification, but all the lighter areas are composed of connective tissue and large cells. X 110.

connective-tissue is increased, and grayish, ramifying streaks are seen, having no relation, however, to the lobular markings. At times the surface is granular and fine hemorrhagic points are noted. The portal vein and hepatic vessels are normal. Enlarged lymph-nodes are often found at the hilus of the liver.

Microscopically, the interlobular connective tissue is enormously increased, although in children some portions of the liver may show but slight involvement. A great number of the characteristic large cells are found in the interlobular tissue, the connective tissue strands being interwoven between the individual cells (Fig. 3). Some of the cells often lose their typical appearance and frequently the interlobular tissue contains long strands and syncytial masses of cells instead of the easily differentiated individual cells. In these situations it may be necessary to employ special stains in order to identify the cells (Fig. 4). The inner portion of the lobules is not usually affected but the invasion of the connective tissue may disturb the peripheral part of the lobules and

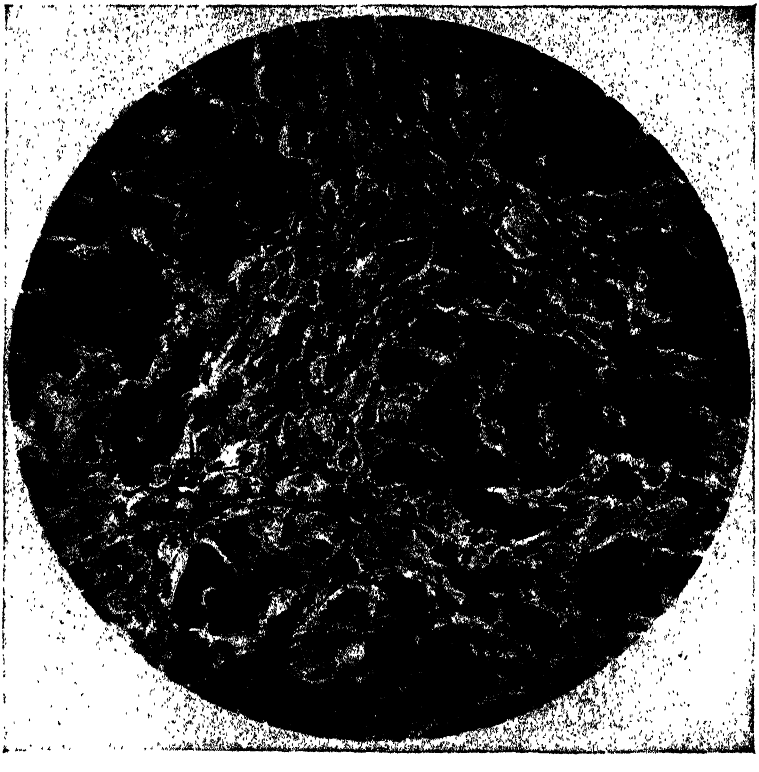


FIG. 4.—MICROSCOPICAL SECTION OF LIVER (High Power).
Showing the relationship of large cells to the connective tissue, also large cells situated in the sinusoids. X 350.

break it up into isolated groups of liver-cells. At times, however, the large cells may extend into the lobule and surround the central vein. The hepatic cells are apparently not affected by the process, but a coarsely granular appearance of the cells has been described, also a moderate grade of fatty degeneration. The characteristic large cells are also found in the sinusoids of the lobules, having been carried here through the splenic vein. The stellate cells of the sinusoids are always normal, however, and apparently take no part in the process. The characteristic cells may be found in the lumen of the larger branches of the portal vein, and groups of these cells have been described in the walls of the veins in the region of the media. Long strands of Gaucher tissue have also been found directly continuous with the fibrous tissue of the adventitia of the veins, proving that the connective-tissue cells of the liver, and of the walls of its veins, may be transformed into the typical large cells. There is no evidence for an endothelial origin of the large cells in the liver and no evidence that the cells proliferate in this organ after being carried through the splenic vein. Recent studies have shown that all the large cells in the liver, apart from those transported from the spleen, have a local origin from modified fibroblasts or reticular cells.

The pigment in the liver is situated in or near the walls of the larger blood-vessels and occasionally in the capsule. It is brownish in color, and shows a positive reaction for iron. In young individuals the pigment may be absent. The bile-ducts are not affected.

LYMPH-NODES.—The superficial lymph-nodes are not appreciably enlarged, but those in the thorax and abdomen are always increased in size, in adults as well as in children. They measure from one-half to two centimeters in diameter and are soft and friable. The color is reddish or brownish-gray in children, and yellow or dark red, or even brownish-black, in adults. On section, the color is pink or reddish and occasionally hemorrhagic markings are seen. The mesenteric and retroperitoneal nodes are relatively larger than the other abdominal lymph-nodes, and the iliac nodes, also those at the hilus of the spleen and liver, as well as those along the splenic vein and in the region of the pancreas, are always appreciably enlarged. The tracheobronchial and esophageal nodes are also increased in size, especially in children.

Microscopical examination shows variations in the degree of involvement in the different regions, the duration of the disease also being an important factor. In most cases the retroperitoneal, mesenteric and iliac lymph-nodes present a more advanced process than the thoracic nodes or the nodes at the hilus of the spleen and liver, although advanced changes have been found in the lymph-nodes at the hilus of the spleen, especially in adult cases. In general, the picture in advanced cases shows marked hypertrophy of the cellular reticulum, a large number of the typical cells, extensive fibrous changes, pigmentation, and a great diminution or complete absence of lymph-adenoid tissue. All stages may be found between this picture and the early lesion in which only a few Gaucher cells may be found in association with changes in the cellular reticulum. The large cells in the nodes, showing an early stage of the disease, are seen as isolated cells without any regular distribution or as small groups in the form of round masses or elongated strands. The latter may often be traced as directly continuous with the surrounding reticulum. The follicles in the early cases are often well preserved, but the germ centers are abnormally large and devoid of lymphocytes and the reticular cells here show active phagocytosis. The lymphocytes of some of the follicles, however, have nearly disappeared and the follicle is represented by a large germ center containing phagocytic reticular cells and surrounded by a fringe of lymphocytes. Some round masses of lymphocytes without germ centers probably represent the remains of follicles. The cellular reticulum of the periphery of the nodules may form a thick wall, and it always shows distinct evidences of hypertrophy in this situation. The reticulum forming the walls of the lymph sinuses and the so-called "endothelium" which lines the sinuses is normal everywhere, and there is no evidence that the Gaucher cells have their origin here. Pigment granules, yellowish-brown in color, giving a positive iron reaction, are distributed in the subcapsular sinuses, along the trabeculæ, in many of the fixed cells of the reticulum and the reticular macrophages, and in some of the large cells. Yellowish, refractive crystals or flakes of pigment, negative for iron, are also present. Phagocytic cells containing erythrocytes are not uncommon, but it has not been decided whether or not these are true Gaucher cells.

In lymph-nodes showing a more advanced stage of the disease, the large cells form large, compact, round or oval masses separated from one another by lymphocytes (Fig. 5). The follicles may be so replaced by the masses of large cells, that the original nature of the tissue cannot be recognized. The cortex is usually packed with masses of Gaucher cells and where the follicles are still preserved the cells occupy the interfollicular tissue between the subcapsular sinuses and trabeculæ, forming an open ring around the follicles. In the medulla the large cells are found in the medullary cords, compressing the sinuses and crowding out the lymphocytes. At times the process is so advanced that no distinction between cortex and medulla can be made. The follicles or their remnants are always surrounded by a ring of large cells and in the center of the follicles large cells are found. Downey has shown that strands of normal reticulum may be traced until they loosen up and assume the identical structure of Gaucher cells, proving that the large cell is merely cellular reticulum modified by the storage of some foreign substance which has been taken up. This accounts for the fusion of Gaucher cells into syncytial masses and for a reduction in the amount of normal reticulum within the masses of Gaucher cells. The sinus walls are always normal and there is no evidence that their endothelial cells are involved in the formation of the large cells. No Gaucher cells are seen within the sinuses. The pigment in the advanced cases shows the same general distribution noted in the early types, but the amount is often so increased that sinuses filled with dark granules may be a conspicuous feature of the histological picture.

BONE-MARROW.—The existence of a lesion was not known until 1904, when the bone-marrow was examined by the authors for the first time and found to contain large cells. The consistency of the bone-marrow is soft and the color is always red, but small white or yellow areas are frequently seen. The large, characteristic cells described in the spleen, liver and lymph-nodes are found here in abundance, where they usually form large compact masses or smaller groups, although isolated cells are also seen. The large cells are found in the very early cases as well as in later life and a close relationship between the cells and strands of reticulum has been observed in all the cases examined (Fig. 6). Pigment granules are rarely found unless the disease has existed for many years. They are seen in the neighborhood of the larger blood-vessels. From what has been described in other hematopoietic organs, it may be assumed that the large cells found in the bone-marrow are also derived from the cellular reticulum, although no particular studies of the histogenesis of the large cells in the bone-marrow have been made.

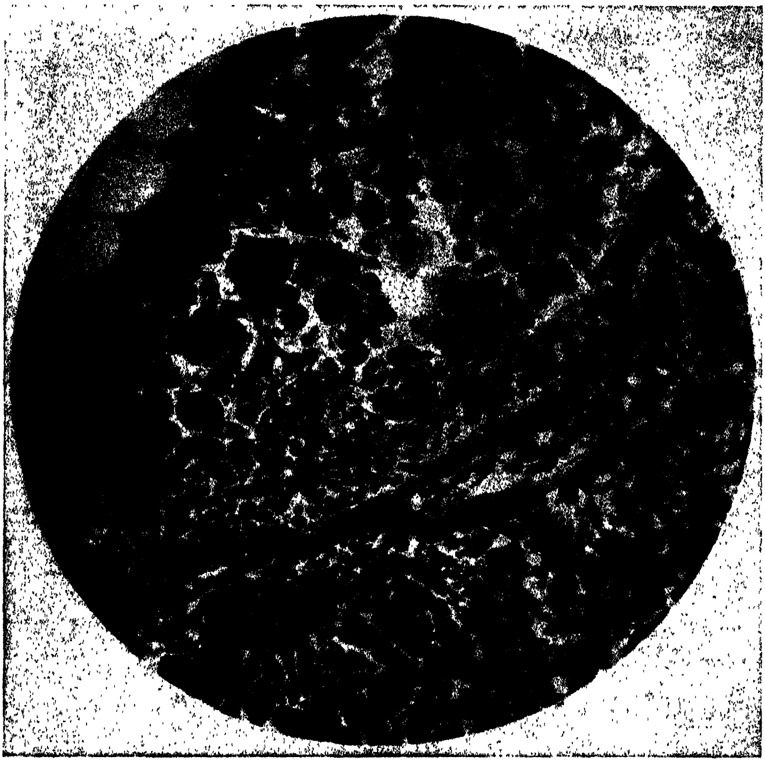


FIG. 5.—MICROSCOPICAL SECTION OF RETROPERITONEAL LYMPH-NODE. Note masses of large cells separated by areas of normal pulp-cells. Several cells with multiple nuclei are seen. X 350.

Other Organs.—In several cases marked hypertrophy of the lymphadenoid tissue of the terminal ileum and cecum has been seen, together with hypertrophy of the germ centers of the follicles, but no Gaucher cells have been found in these situations. Lesions in other organs and tissues have also been described, such as pigmentation of the muscle fibers of the intestine, hemorrhage and pigmentation of the thigh muscles, pigment in the uterus and salivary glands, but none of these lesions are constant, nor do they have any bearing on the distinctive pathological features of the disease. In a case reported by Marchand, a few characteristic large cells were found in a connective tissue septum of the thyroid gland, near a small collection of lymphoid cells. It is most probable that the latter represented misplaced lymphoid tissue and that the large cells were derived from the reticulum of this tissue, rather than from the thyroid gland itself.

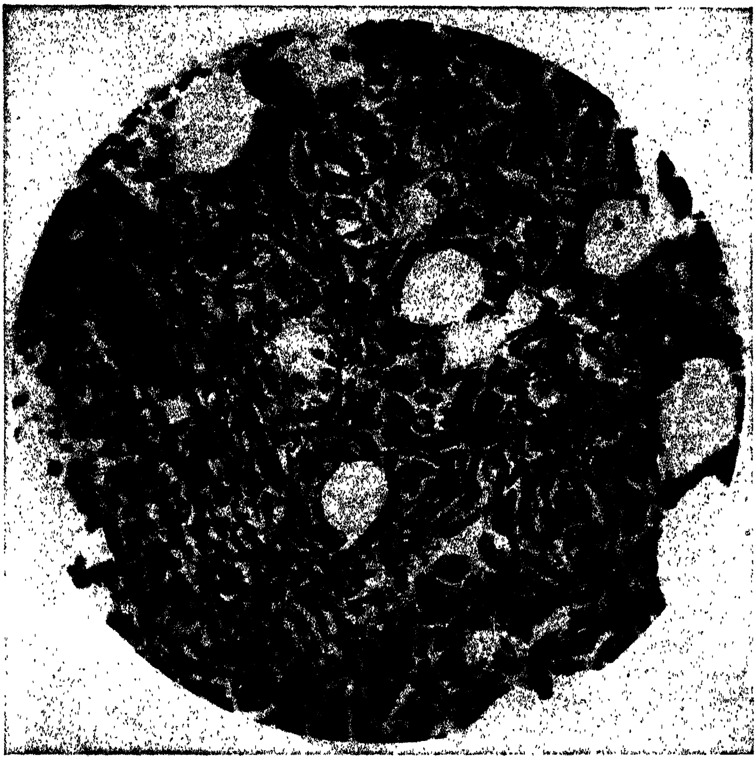


Fig. 6.—Microscopical Section of Bone-Marrow (High Power).
Most of the field is occupied by large cells somewhat compressed and elongated. X 350

In several authentic cases of Gaucher's disease, local or disseminated foci of tuberculosis have been described. These lesions are always superimposed and have no bearing upon the pathological process.

PATHOLOGICAL CONDITIONS SIMULATING GAUCHER'S DISEASE.—It is well known that certain groups of cells, especially the reticular cells of hematopoietic organs, are affected by the action of various agents, chemical, bacterial, toxic or metabolic in nature, the reaction depending in each instance upon the nature of the irritant. Many of these agents are capable of producing cellular reactions, which, in some instances, may bear a striking resemblance to the histological picture of Gaucher's disease. Thus, the injection of carmin or acid colloidal dyes into animals (vital staining), or the feeding of animals with cholesterin or fatty substances, produces changes in the same specific group of cells which are concerned in Gaucher's disease, and in the animal-feeding experiments, the resemblance is most marked. The large cells in the latter condition, however, contain fatty or lipoid substances, which are never found in Gaucher's disease, and other distinctive features seen in the Gaucher cells are lacking as well. Furthermore, experimental bacteriemia may be followed by a marked activity of the reticular cells, and the toxin produced by the typhoid bacillus or the tubercle bacillus may cause cellular reactions in the same cells. In all of these conditions, however, careful histological or microchemical studies of the tissues always reveal variations in the character of the reactions and important differences in the nature of the cells. These cells have been classified by various authors as endothelial leukocytes, histiocytes, pyrrhol cells, resting wandering-cells, macrophages or cholesterinesterphagocytes.

In recent years a few cases of diabetes associated with lipoidemia have been reported in which cellular hyperplasia was noted especially in the spleen, but other organs, such as the liver, lymph-nodes and adrenals, were involved in one case, and the aorta in another instance. In these cases the presence of anisotropic bodies and lipoid substances in the large cells was established. It is quite evident, from the few examples cited, that the simple presence of large cells in hematopoietic or other organs does not constitute Gaucher's disease and it is also apparent that the histopathology and microchemical features of the large cells must always depend upon the etiological factors concerned.

Historical Summary.—Under the title "De l'épithéliome primitif de la rate," Gaucher reported the first case of this disease in 1882. The patient was a woman, aged 32 years, whose spleen had been enlarged for 25 years. The patient died as the result of a pulmonary tuberculosis. The autopsy revealed a spleen weighing 4,770 grams and a large liver, also tuberculosis of both lungs and peritoneum. Gaucher states that the spleen pulp was replaced by large, nucleated epithelial cells, round or polyhedral in shape, with homogeneous, opaque, poorly-staining protoplasm lying in well-defined alveolar spaces. The connective tissue stroma was increased and no Malpighian bodies were visible. He regarded the case as a primary epithelioma of the spleen, and described the lesion in the liver as a diffuse interstitial cirrhosis.

Collier, in 1895, reported the case of a girl, aged 6 years, with a history of splenic hypertrophy for 4 years. Death resulted from bronchopneumonia. The spleen at autopsy weighed 4 pounds and the mesenteric lymph-nodes were enlarged. Microscopically, the characteristic lesion was found in the spleen and lymph-nodes, and the author considered the case to be one of endothelioma. An older sister died at the age of 8 years, and a spleen weighing 25 ounces was found, but there is no report in her case of a microscopical examination.

In the following year Picou and Ramond reported the case of a woman, aged 32 years, who complained of abdominal pain following trauma to the abdomen four years previously. She was operated upon for uterine fibroids, but a large spleen was found and removed, and the patient recovered. The spleen weighed 2,800 grams. The histological picture in the spleen was typical and the enlarged lymph-nodes at the hilus showed the characteristic lesion. The authors decided that the case was a primary epithelioma of the spleen with secondary involvement of the lymph-nodes. Cornil, discussing this case, considered the process as a primary hypertrophy of the spleen with proliferation of the reticulum.

Bovaird, in 1900, reported the first case in this country. The patient was a female, aged 16, with a history of splenic hypertrophy of 13 years' duration and a typical clinical picture. A splenectomy was performed, the patient dying three hours later. The spleen weighed 12½ pounds, the liver, 4¼ pounds, and the mesenteric lymph-nodes and those at the hilus of the spleen were enlarged. After a careful histological examination in which the lesions in the spleen, liver and lymph-nodes were accurately described, Bovaird concluded that the disease was not an endothelioma of the spleen with metastases in the liver and lymph-nodes, but considered the process to be "a hyperplasia of the spleen characterized by an unusual development of endothelial cells and the transformation of a considerable part of the organ into dense connective tissue." The lesion in the liver and lymph-nodes was also considered to be an endothelial hyperplasia, confined in the liver to the lymph spaces in the perilobular connective tissue. A younger sister was under observation between her third and sixth years; she had a palpable spleen and liver, distinct bronzing of face and hands and frequent epistaxis. The author drew attention to the occurrence of these 2 cases in one family and stated that this feature "certainly suggests the action of some systemic poison affecting several members of a family."

Brill, Mandlebaum and Libman, in 1904, reported the first male case in the literature. The patient, and three sisters, all affected with splenic hypertrophy, had been under Brill's observation for 19 years. Profiting by the autopsy report of the case reported by Bovaird, Brill, in 1901, was able to isolate these 4 cases from the large unclassified group of splenic enlargements, to place them in a separate group, and to establish for them a distinct clinical picture. The autopsy on the male case mentioned above, as well as the autopsy on one of the female members of this family, five years later, confirmed his diagnosis. The male patient was 34 years of age and an enlargement of the spleen had been noted for 15 years. In this case epistaxis was a marked feature, and ecchymoses on the legs and hemorrhagic furuncles occurred from time to time. Death followed an attack of hemorrhagic pericarditis. The spleen weighed 5,280 grams, the liver weighed 4,800 grams, and the mediastinal and abdominal lymph-nodes were moderately enlarged. The histological picture was typical of the disease and the presence of large cells in the bone-marrow was noted in this case for the first time. The authors stated that the large cells arose directly from the endothelial lining of the pulp spaces of the spleen.

In 1907, Schlagenhaufer reported the case of a woman, aged 41 years, with a history of abdominal enlargement for 36 years. In this family two sisters also had well-marked splenic hypertrophy. The patient died of a generalized tuberculosis. At autopsy the spleen weighed 3,510 grams, the liver 3,000 grams, and the microscopic picture of the hematopoietic organs was characteristic. Miliary tuberculosis was described in the submaxillary lymph-nodes, spleen, liver and bone-marrow. The author considered the process to be a systemic disease of the "lymphatic-hematopoietic" apparatus with proliferation of the reticulum. At first he looked upon the tuberculous lesions as secondary, but finally decided that some toxin, probably of a tuberculous nature, was the most probable etiological factor.

In the following year, Von Herczel described the case of a woman, aged 37 years, with a history of an enlarged abdomen for 4 years. The patient recovered after a splenectomy. The spleen weighed 3,000 grams and presented the typical microscopic picture of the disease, but the author failed to classify the lesion, which he thought to be an inflammatory process or a new growth. The slides were subsequently examined by Risel, who established the correct diagnosis.

Marchand, in 1907, reported the case of a woman, 44 years of age, who gave a history of splenic hypertrophy of 9 years' duration. Death was ascribed to asthenia. In this case the spleen weighed 2,720 grams. The liver was enlarged, but the weight was not given. The histological picture is typical of the disease, and Marchand stated that the large cells might originate either from reticulum or endothelium. He looked upon the process as a deposit in the cells of some unidentified foreign substance and not as an ordinary hyperplasia or a tumor. Risel, subsequently (1909), made an exhaustive study of the material from this case and stated that the large cells probably have their origin in the reticulum of the lymphatic hematopoietic system, the lymph-adenoid tissue not being affected. He maintained that the cells in the lymph-nodes may arise late in the course of the disease from the endothelium of the lymph sinuses as well as from the intrafollicular reticulum, and that the cells are brought to the capillaries of the liver through the portal vein. He could not explain the presence of the cells in the connective tissue spaces of Glisson's capsule, nor was it easy to account for the cells within the venous sinuses of the spleen, if they had their origin in the reticulum. He suggested, however, that the walls of the splenic sinuses might be injured by the enormous swelling of the reticulum and that openings might result through which the cells could pass into the sinuses. Although Risel could find no positive evidence of direct transition of reticulum into large cells, he believed, nevertheless, in their reticular origin, without any definite proof.

In 1909, Brill, Mandlebaum, and Libman reported their second case, a sister of the patient whose case was previously described. She was 37 years of age and the splenic enlargement was first discovered when she was 21. The clinical history conforms to the other cases in the literature, but a tendency to severe hemorrhages was a prominent feature. Death resulted from a fracture of the skull due to an accident. The spleen weighed 7,400 grams, the liver, 3,900 grams. The histological picture was typical, but the pigment, especially in the abdominal lymph-nodes, was more prominent than usual. The authors stated that the large cells were derived from endothelium or normal reticulum, and called attention to the susceptibility of these tissues to some unknown toxic agent. Tuberculosis, when present in cases of Gaucher's disease, must be considered as a superimposed process.

In 1910, de Jong and van Heukelom reported a splenectomy in a female, 12½ years of age, with enlargement of the spleen and liver for 5 years. There were ten children in the family and a sister of 18 and a brother of 15 were similarly affected. The diagnosis of Gaucher's disease was made before the operation and was subsequently confirmed by histological examination. The patient made a good recovery. The spleen weighed 1,850 grams and the microscopic picture was typical. The authors decided that the large cells were derived from reticulum, stating, however, that the possibility of an endothelial origin could not be denied. As the liver, in their patient, continued to enlarge after the operation, the theory was advanced that the cells carried to that organ through the portal vein must have the power of multiplying, but the fact that large cells are also present in the interlobular connective tissue of the liver was not discussed.

Two years later, Mandlebaum reported the second male case in the literature, a boy 4½ years of age with a large spleen noted for one year, the correct diagnosis being established clinically. Two sisters in this family were also the subjects of splenic hypertrophy. The patient died following a splenectomy. The weight of the spleen was 490 grams, of the liver, 730 grams. The histological features in the hematopoietic organs were typical and a special study was made of the follicles and germ centers in the lymph-nodes, drawing attention to the peculiar changes in the germ centers and the phagocytic cells present. It was assumed that the large cells arose in this situation, but the author could not decide whether these cells were specific lymphoid elements, whether they were derived from the reticular cells of the germ centers, or whether they were cells of unknown origin. It was thought that the large cells in the spleen were not derived from endothelium, as originally stated, but from the reticulum. The nature of the cytoplasm could not be determined by chemical reagents or by staining methods. Attention was called to a family predisposition to some toxic agent causing an irritability of the follicles in the hematopoietic system.

Downes, in 1913, reported the case of a woman, aged 28 years, with a history of splenic hypertrophy for 15 years. A splenectomy was performed and the patient made a good recovery. The spleen weighed 1,813 grams and showed the typical lesion. The process was described as an extensive, uniform, diffuse endothelial hyperplasia. The sinus endothelium was reported as hypertrophic but not actively proliferating. No comments were made in reference to the origin of the large cells.

In the same year Wilson described the histological findings in the spleen removed from a woman, aged 27 years, with a history of splenic hypertrophy of 15 years' duration. The patient died after the operation. The spleen was typical of the disease and weighed 5,280 grams. The author considers the process to be "a primary endothelial proliferation with a secondary proliferation of fibrous connective tissue, and ultimately a degeneration of the endothelium with contraction of the connective tissue." He favors the endothelial, rather than the reticular, origin, of the large cells.

Sapegno, in the same year, reported the case of a man, 47 years of age, with a history of chronic pulmonary disease and enterocolitis. At autopsy the spleen weighed 760 grams; the liver and the mesenteric lymph-nodes were enlarged. The histological picture in these organs is typical and the characteristic large cells were also found in the bone-marrow. The author states that the large cells are probably derived from the reticulum.

Stevenson, in the same year, reported the case of a woman, 22 years of age, with a history of epistaxis. An enlargement of the liver was noted at the age of 9 years, and at the age of 22 years the lower border was felt two inches below the ribs. At the same time the spleen extended nearly to the umbilicus. Ten months later the spleen extended three inches below the umbilicus and into the pelvis. The red blood-cells were considerably diminished and a slight leukopenia was noted, the differential leukocyte count being normal. No skin pigmentation was observed. A splenectomy was performed and the patient recovered. Two weeks later pigmentation of the face was noted. The spleen weighed about 6 pounds and measured 33 cm. The microscopic examination of the spleen is not mentioned in the paper, but the photomicrograph accompanying the article is typical of the disease. This, in conjunction with the suggestive clinical history, seems to warrant the diagnosis of Gaucher's disease.

In 1914, Erdman and Moorhead reported a successful splenectomy in the case of a female infant 3½ years of age, with an enlarged spleen discovered at the age of 1 year. The spleen weighed 430 grams and presented the typical lesion of Gaucher's disease. A few miliary tubercles were found in the sections. In the opinion of the authors the large cells are of endothelial origin, on account of the "morphological appearance of the cells and the swollen condition of the endothelium of the small vessels."

Niemann, in 1914, reported the case of a female infant, 17 months of age, with rickets, positive Wassermann reaction, pigmentation of the face, and marked enlargement of the spleen and liver, noted since she was two months of age. At autopsy the spleen and liver were greatly enlarged and the histological description is that of Gaucher's disease. The lymph-nodes were also characteristic, but the bone-marrow was not examined. None of the organs presented any evidence of syphilis. Niemann unfortunately did not classify the case as one of Gaucher's disease, being unaware of the existence of this disease in infants. It was published with the title: "Ein unbekanntes Krankheitsbild" (An Unknown Type of Disease), even though the resemblance to Gaucher's disease was noted by the author.

In 1914, Herrman, Roth and Bernstein reported the case of a boy 14 years of age with enlargement of the spleen for 10 years and a typical clinical history. The correct diagnosis was established, and the patient recovered after splenectomy; the spleen weighed 1,320 grams. The histological examination showed the characteristic lesion, but no opinion was given in regard to the histogenesis of the large cells.

In 1915, Bernstein showed that the diagnosis of Gaucher's disease could be definitely established by puncture of the spleen and microscopic examination of the aspirated pulp. This was done just before operation in the case of a girl, 7½ years of age, a sister of the patient reported by Herrman, Roth and Bernstein with a history of enlargement of the abdomen for one year. The characteristic large cells were found in the aspirated fluid, and the spleen, which weighed 620 grams, presented the typical features of the disease. This patient was successfully operated upon by Syms, but the case has not been reported in full as yet.

In 1916, Mandlebaum and Downey published the results of an investigation to determine the origin and nature of the large cells of Gaucher's disease, employing the material obtained from the boy whose case had been reported in 1912. They were able to show conclusively that the large cells arise from the reticular apparatus of the hematopoietic organs, but could not deny that the endothelial cells of the venous sinuses in the spleen might not participate in the formation of the free cells in the sinuses. The authors also proved that fat or lipoid substances cannot be found in the large cells of Gaucher's disease by microchemical or polariscopic examination. They stated, as the result of a chemical analysis of the spleen, that the peculiar substance in the large cells may be of complex protein nature, probably in combination with the phosphatids.

The authors drew attention to certain other conditions characterized by the presence of large cells in the spleen and other organs, the general distribution of the cells being quite similar to that found in cases of Gaucher's disease. In vitally stained animals, or in animals fed upon fatty substances or cholesterin, for example, the same specific group of cells is involved, and in cases of diabetes associated with lipoidemia, the histological resemblance to Gaucher's disease is quite striking. The authors, however, were able to show the marked differences in the character of the cells in these various conditions and to disprove the statement of those who have claimed the identity of Gaucher's disease with lipoidemia. They stated that the disease is evidently caused by some metabolic disturbance, the products being found in a specific group of cells, the reticulo-endothelial cells or reticular phagocytes of the hematopoietic organs.

Later in the same year, Evans reported the case of a boy, 4 years and 11 months of age, with an enlargement of the spleen discovered at the age of 2 years, and progressive cerebral symptoms for one year, leading to a fatal termination. The histological findings were typical of Gaucher's disease, but the changes in the liver showed a somewhat early type of lesion. The author states that the cells are identical with the vitally-staining reticulo-endothelial cells, but the agent exciting the great proliferation of these cells in Gaucher's disease is not known. He also believes that careful metabolic studies on cases of Gaucher's disease might be of value in throwing light on the etiology.

In 1918, Reuben reported the case of a male infant, 2 years of age, with the history of abdominal enlargement for 18 months. The hypertrophy of the spleen, in association with epistaxis, discoloration of the skin and other clinical factors, led to a tentative diagnosis of Gaucher's disease, which was definitely established after aspiration of the spleen.

A report of two adult cases, studied by Mandlebaum (1918), is being prepared for publication. The first case, that of a woman, 41 years of age, with a history of splenic hypertrophy for 35 years, was successfully operated upon, and the spleen, which weighed 4,250 grams, showed the typical histological picture. The diagnosis was made prior to operation from the history and the physical findings. The second case occurred in a man, 37 years of age, with enlargement of the abdomen noted for 12 years. This patient died 18 days after a splenectomy; the spleen weighed 3,500 grams. The clinical picture in this case was also characteristic and the correct diagnosis made before the operation. The autopsy findings were typical of Gaucher's disease, except that the liver was not appreciably enlarged. Microscopical examination of the liver, however, showed the characteristic lesion. In a discussion of the histogenesis and nature of the large cells, the author corroborates the result of the investigation of Mandlebaum and Downey.

From time to time authors have reported, as instances of Gaucher's disease, cases of splenomegaly unattended by the clinical and pathological factors which characterize this disease. It has repeatedly been shown that the clinical picture of Gaucher's disease is distinctive, that the pathological histology is definite and characteristic; nevertheless some authors have confused the subject by an utter disregard of the factors so fully described in the literature. The cases lacking scientific proof as to their genuineness have been analyzed by Brill and Mandlebaum (1913) and by Mandlebaum and Downey (1916).

BIBLIOGRAPHY

BERNSTEIN, E. P. Gaucher splenomegaly diagnosed by spleen puncture before operation. Jour. Am. Med. Assn., 1915, lxiv, 1907.

BOVAIRD, D., JR. Primary splenomegaly—endothelial hyperplasia of the spleen—two cases in children—autopsy and morphological examination in one. Am. Jour. Med. Sc., 1900, cxx, 377.

BRILL, N. E. Primary splenomegaly. With a report of three cases occurring in one family. *Ibid.*, 1901, cxxi, 377.

BRILL, N. E., MANDLEBAUM, F. S., AND LIBMAN, E. Primary splenomegaly—Gaucher type. Report on one of four cases occurring in a single generation of one family. *Ibid.*, 1905, cxxix, 491.

——— Primary splenomegaly of the Gaucher type. A report on the second of four cases occurring in a single generation of one family. *Ibid.*, 1909, cxxxvii, 849.

BRILL, N. E., AND MANDLEBAUM, F. S. Large-cell splenomegaly (Gaucher's disease): A clinical and pathological study. *Ibid.*, 1913, cxlvi, 863.

COLLIER, W. A. A case of enlarged spleen in a child aged six. Tr. Path. Soc. London, 1895, xlvi, 148.

DOWNES, W. A. Primary splenomegaly of the Gaucher type; report of a successful splenectomy. Med. Rec., 1913, lxxxiii, 697.

ERDMANN, J. F., AND MOOREHEAD, J. J. Splenectomy for splenomegaly (Gaucher type). Am. Jour. Med. Sc., 1914, cxlvii, 213.

EVANS, F. A. Gaucher splenomegaly in a child. Proc. New York Path. Soc., 1916, xvi, 114.

GAUCHER, E. De l'épithélioma primitif de la rate. Thèse de Paris, 1882.

v. HERCZEL, E. Ueber eine bisher unbekannte Ursache des Fiebers nach Milzexstirpationen. Fall 4: mit Leberhypertrophie verbundene Splenomegalie, Milzexstirpation (Heilung). Wien. klin. Wchnschr., 1907, xx, 127.

HERRMAN, C., ROTH, H., AND BERNSTEIN, E. P. A case of Gaucher's disease in a boy thirteen years of age. Splenectomy with recovery. Arch. Pediat., 1914, xxxi, 340.

DE JONG, R. DE J., AND VAN HEUKELOM, J. S. Beitrag zur Kenntnis der grosszelligen Splenomegalie (Typus Gaucher). Ziegler's Beitr., 1910, xlviii, 598.

MANDLEBAUM, F. S. A contribution to the pathology of primary splenomegaly (Gaucher type), with the report of an autopsy on a male child four and one-half years of age. Jour. Exper. Med., 1912, xvi, 797.

——— Two cases of Gaucher's disease in adults: A study of the histopathology, biology and chemical findings. Am. Jour. Med. Sc., 1919, clvii, 366.

MANDELBAUM, F. S., AND DOWNEY, H. The histopathology and biology of Gaucher's disease (large-cell splenomegaly). Folia haematol., Arch., 1916, xx, 139.

MARCHAND, F. Ueber sogenannte idiopathische Splenomegalie (Typus Gaucher). Münch. med. Wchnschr., 1907, liv, 1102.

PICOU, R., AND RAMOND, F. Splénomégalie primitive, épithélioma primitif de la rate. Arch. de méd. expér. et d'anat. path., 1896, viii, 168.

NIEMANN, A. Ein unbekanntes Krankheitsbild. Jahrb. f. Kinderh., 1914, lxxix, 1.

REUBEN, M. S. Gaucher's disease. New York Med. Jour., 1918, cvii, 118.

RISEL, W. Ueber die grosszellige Splenomegalie (Typus Gaucher) und über das endotheliale Sarkom der Milz. Ziegler's Beitr., 1909, xlvi, 241.

SAPEGNO, M. Contributo allo studio delle malattie sistematiche dell'apparato emopoietico. "La splenomegalia tipo Gaucher." Arch. sc. di med., 1913, xxxvii, 323.

SCHLAGENHAUFER, F. Ueber meist familiär vorkommende, histologisch charakteristische Splenomegalien (Typus Gaucher). (Eine Systemerkrankung des lymphatisch-hämopoetischen Apparates.) Virchow's Arch., 1907, clxxxvii, 125.

Stevenson, Sir E. S. Splenomegaly. Brit. Med. Jour., 1913, ii, 847.

Wilson, L. B. The pathology of splenomegaly: A study of the operative and autopsy material from the Mayo Clinic. Surg. Gyn. and Obstet., 1913, xvi, 240.

CHAPTER V

DISORDERS OF THE PITUITARY GLAND

(*Hypophysis Cerebri*)

BY WM. ENGELBACH, B.S., M.S., M.D.
and
JOHN L. TIERNEY, A.M., M.D.

Lobar Function Classification.—The heterogeneous classifications of the numerous types of diseases of the pituitary gland have been an impediment to the very interesting study of these dyscrasias. The following facts would tend to justify an entirely new grouping of these diseases. There is no single classification which has been adopted by any authority except its originator, and all those which have been advanced to date have been admittedly crude and insufficient to qualify as a grouping system of the many aberrant and distorted clinical syndromes. Cushing, in his remarkable "Monograph on Disorders of the Pituitary Gland," undoubtedly projected the knowledge concerning the diseases of this gland more than the work of any author to date. Concerning classification, he states: "We are unquestionably approaching a stage in our knowledge when classification or grouping of these cases here employed, as a provisional basis for clinical use, will no longer be necessary. However, it may temporarily serve others as it has served us, and some one, it is hoped, will provide a more useful subdivision, if a subdivision is at all necessary. That there are obvious crudities in this provisional method of grouping these patients, is freely acknowledged." He divided his material into five groups, as follows:

GROUP I: Cases of dyspituitarism in which not only the signs indicating distortion of neighborhood structures, but also the symptoms betraying the effects of altered glandular activity are outspoken.

GROUP II: Cases in which the neighborhood manifestations are pronounced, but the glandular symptoms are absent or inconspicuous.

GROUP III: Cases in which neighborhood manifestations are absent or inconspicuous though glandular symptoms are pronounced and unmistakable.

GROUP IV: Cases in which obvious distant cerebral lesions are accompanied by symptomatic indications of secondary pituitary involvement.

GROUP V: Cases with a polyglandular syndrome in which the functional disturbances on the part of the hypophysis are merely one, and not a predominant feature of a general involvement of the ductless glands.

The first three groups he subdivides into: (1) hyperpituitarism (Typus Launois and Marie); (2) hypopituitarism (Typus Froehlich); (3) dyspituitarism, perverted pituitary function consisting of mixed or transient cases exhibiting some features of both states.

This, as well as all previous classifications, fails to take into consideration the marked difference in function of the *two lobes* of the pituitary body, *i. e.*, they are all based upon what are considered disturbances of function and consequent secretions of the *entire gland.* While it is true that nearly all authors mention the fact that frequently only one lobe of the gland is involved and report such cases, yet there is no classification of *one-lobe* affections of the pituitary gland. Some authorities group these cases with the large division of pituitary deficiency, other authors with overactivity of the pituitary, but the majority class them with perverted or mixed secretory lesions under dyspituitarism. Whether the time has arrived to accept the known physiological and clinical hormonic signs as sufficient basis for separating the pituitary into two distinct lobes is questionable. This has been suggested by a number of authors; for instance, Cushing states that the striking fault in the classification to the date of his monograph (1910) lies in the fact that the dualistic character of the gland was not taken into consideration. He says:

"We may doubtless have either an over- or an underactivity both of the anterior and the posterior lobes, or of either one alone. Hence, there occur in our series individuals whose overgrowth suggests a former state of glandular overactivity of *one* or possibly of *both lobes,* but who in time have acquired evidences of insufficiency of *both lobes* or of the *posterior lobe alone.* But in the present state of our knowledge of the different rôles played by the two lobes in disease, it would be unsafe in many instances to draw conclusions as to their individual participation in the given syndrome."

Another very important point, first described by Marie (1889) but more recently applied, is the *marked change of the state and degree of function* which these cases undergo *during their course.* For instance, it is now a well-known fact that nearly all the cases of hyperfunction, producing hypersecretions of both or either lobe of the pituitary gland, in the course of a short time *changed into exactly the opposite state of function,* that of hyposecretion. This fact forcibly demonstrates the need of placing these diseases on the basis of the functional activity of the separate lobes or of the entire gland, and that this function or state of secretion *must be determined at the time of observation.* For instance, the diagnosis cannot be made upon such signs as skeletal over- or undergrowth, function of the genitalia, or obesity, which may be clinical signs resulting from *years precedent* secretory disturbance of one or both lobes—the gland or one lobe *at the time of observation being in the exact opposite state of activity* to that indicated by these hormonic signs. If the present state of rapidly accumulating knowledge regarding the entire system of ductless glands is of any value at all, it must be based upon precepts which would dictate that *certain* definite *changes,* occurring in the entire pituitary or in its lobes, at a *certain time* in the *development* of the *individual,* will *always produce exactly the same physical and metabolic abnormalities of the individual.* There is no question that in the classical varieties of these diseases, involving both lobes of the gland, this has been repeatedly proven by the large number of controlled cases in literature. This same fact must pertain to those less marked or incomplete forms of pituitary dyscrasia involving either one or both lobes, varying only in degree from the complete forms involving the entire gland. Yet we find the most positive types of *insufficiencies of one lobe* (posterior) of this gland classified by some under hyperpituitarism, by others under hypopituitarism, and yet by others under dyspituitarism. These same authors admit, in discussing these cases, that the evidence in many of them points to the involvement of only a single lobe of the hypophysis and that the lobe at the time of observation has just the opposite activity to the group under which they have classified the case. This occurs because the majority accept the hormonic changes of the skeleton, metabolism, obesity, the genitalia, the dermal system, etc., as the best evidence for classification. The *manifestations of activity or inactivity* of the gland which are *present at the time of observation,* are not given sufficient consideration. For this reason a great many cases which are really hyposecretory diseases have been classified among hypersecretory groups, merely because they were originally diseases of overactivity, which have changed to a decided inactivity. A great majority of those cases *involving only one lobe* of the gland, either the anterior or the posterior, have been classified among the dyspituitarisms, for the very reason that there was not sufficient evidence to demonstrate either an overactivity or an inactivity of *both* lobes of the gland. The variation in degree—whether the entire gland or only one of its lobes is only *slightly* inactive, or overactive, or *decidedly* hypo- or hyperfunctionating—is another fact which modifies the entire clinical picture so decidedly that the minor, aberrant, incomplete or intermittent disturbances of secretion have undoubtedly been constantly overlooked. It is possible that the separation of the diseases of the two lobes of the gland into corresponding groups or varieties will, in the course of time, cause the term "dyspituitarism" to be entirely disregarded.

AGE.—The fact that the *same* disturbance of function of the pituitary gland, occurring at *different times in life,* causes such a decided difference in the clinical manifestations of the patient, is accountable for some of the difficulties in grouping these dystrophies. The typical adiposity, associated with hypoplasia of the genitalia, has been considered the essential sign of hypopituitarism. Consequently it did not become known, until Lorain described the non-obese type existing in the primary, pre-adolescent hypopituitarism, that all these cases were *not* associated with *marked adiposity*. The difference in the skeletal growth in cases occurring at different ages, has also been disconcerting to many clinicians. Why certain types of this disease, due to the *same cause* of hypofunction of the gland, were extremely tall, while others were short, having a typical, retarded skeletal growth, has not been sufficiently explained.

TUMOR.—That a small percentage of the typical cases have large *pituitary neoplasms* producing enlargement of the sella turcica and intracranial pressure signs is well known, but that a large majority have a pituitary gland decreased in size and shape, clinically, or even as to macroscopic pathological changes, is not appreciated.

Anatomical Consideration of Individual Lobes.—*Structure.*—The question arises, whether the remarkable amount of scientific evidence, evolved during the last few years, has advanced the knowledge of the functions of the individual lobes of this gland sufficiently to allow the absolute separation of this gland into its two different lobes, from the standpoint both of function and of constitutional hormonic effects. The correlation of the action of the secretions of these two lobes, with the clinical signs of their effects upon the organs and the metabolism of the body, particularly the skeleton, the genital tract, adiposity, blood-pressure, temperature, and involuntary muscle contractions, is convincingly proven. It is well known that the pituitary gland is really not a single gland. Embryologically, it is derived from two entirely different tissues, the anterior lobe from the solid epithelial process of the Rathke pouch and the posterior lobe from the diencephalon. Histologically, it is made up of entirely different structures. The posterior lobe (pars nervosa) is composed almost entirely of neurological tissue, the anterior lobe (pars glandularis) of chromaffin tissue. The pars intermedia, or infundibulum, is assumed by the writers to belong to the posterior lobe. The functions of the two lobes are as different as their origins. While there is undoubtedly much to be learned regarding the physiology and the hormonic effects of the lobes of the hypophysis, on the other hand there is enough absolute knowledge concerning some of the most important functions of each lobe (anterior and posterior) to justify the use of their functions as the foundation for at least a simple, and, let us hope, an accurate anatomico-physiological classification of diseases of this gland.

The *functions* of the individual lobes of the pituitary gland, acting through their secretory hormones, which have been unquestionably established, are as follows: (1) The anterior lobe regulates and controls (*a*) the skeletal growth, and (*b*) the function and development of the gonads and the secondary sexual characters. (2) The posterior lobe is definitely concerned with (*a*) the regulation of the carbohydrate metabolism—glycosuria, hyperglycemia, sugar tolerance, and obesity; (*b*) the contraction of involuntary and unstriped muscles—peristalsis and uterine contraction; (*c*) the renal secretions—polyuria; (*d*) the blood-pressure; and (*e*) the body temperature. There are undoubtedly many other functions possessed by both these lobes of the hypophysis. They are so indefinite, however, as not to be very valuable as clinical evidence of disturbances of activity of the individual lobes of this gland. It is true that this gland is not alone involved in performing the above functions. For instance, the skeletal growth is undoubtedly, during a certain age, dependent upon the hormones of the thyroid, and possibly of the thymus. The cortex of the adrenal, without question, furnishes an exciting secretory hormone for the development and function of the genitals. Carbohydrate metabolism, involuntary muscle contractions, blood-pressure, etc., are probably affected by other internal secretions. Yet the secretions of these two lobes of the pituitary are so specifically connected with the systems and functions mentioned above, that very reliable physical and chemical changes in them take place when even moderate disturbances of function, over- or inactivity of these lobes, occur. Other ductless glandular diseases affecting these organs and the metabolism, will be differentiated by their many other clinical manifestations and complexes.

The clinical syndromes (exclusive of pituitary neighborhood signs and symptoms), formerly termed "glandular" symptoms, are named "hormonic" signs and symptoms, a qualification applying to all endocrine disorders. The "hormonic" signs and symptoms are defined as physical or metabolic changes associated with other endocrine symptoms due to an abnormal secretion of a ductless gland. Those pertaining to the pituitary disorders are divided into the physical, metabolic, and other endocrine symptoms. The physical "hormonic" signs are subdivided into the general and regional.

Among the general "hormonic" signs are the well-known changes in osseous development, producing classical disproportion in the measurements (torso, lower measurement, and span), unusual development of the voluntary musculature, abnormal contraction of the unstriped muscle-tissue, pigmentation, and hair distribution. Among the significant regional "hormonic" signs are local changes in the head, nose, teeth, chin, hands, and genitalia, localized adiposity, pigmentation, etc. Other important pituitary endocrine symptoms are polyuria, glycosuria, hyperglycemia, changes in basal metabolism, carbohydrate tolerance, mentality, other endocrine secretions, temperature, pulse, and blood-pressure.

Certain combinations of the above "hormonic" signs and symptoms are taken as indicative of abnormal secretion of an individual lobe or of both lobes of the pituitary gland. These combinations or clinical syndromes were present so constantly in classical types and varieties of pituitary disorders, that they have been deemed the most valuable as a grouping system for these diseases. The neighborhood signs and symptoms, while important as diagnostic evidence of the neoplastic varieties of the disorders, were of little value in differentiating the varieties and types for the purpose of classification or diagnosis. This is true on account of the fact that pituitary tumors were found associated with all the various clinical syndromes. Furthermore, the incidence of pituitary tumor was so rare (6 per cent. of the cases herewith reported) that its symptomatology was practically useless as a basis for general classification. The histopathology of the hypophysis, particularly of the aneoplastic type, has been too poorly defined to make it a dependable basis worthy of classification.

If these so-called atypical, aberrant or mixed secretory anomalies of this gland were taken out of the various divisions into which they are classed at the present time and re-grouped into unilobar or bilobar subdivisions, this would undoubtedly project (*a*) a more careful study of the physiological functions of the individual lobes of this gland; (*b*) a more precise correlation of the hormonic effects of the respective secretions of each lobe, as well as of the entire gland; and (*c*) result in a more rapid development of the early diagnosis and treatment of pituitary dyscrasias. The last argument alone is sufficient to justify an attempt to form a new grouping of these diseases, *based upon the functions existing at the time of observation of the individual lobes of the pituitary gland.* A point of contention which naturally arises is (1) whether there are a sufficient number of cases involving only *one lobe* of the gland, convincingly established, to justify such a redivision, and (2) whether, on account of their intimate anatomical relationship, it is possible for *one lobe* of the pituitary gland to be decidedly disturbed in function or secretion, without affecting the other lobe. Time, experimentation, and more thorough clinical investigation will decide this question. Very careful and prolonged observation and analysis of personal cases, in the series reported herewith, as well as a careful analysis of many cases in literature, indicate that both these points of contention will be disqualified. Respecting the foregoing contention and forthcoming criticism with the above conclusive functions of the individual lobe as a basis for reclassification of these diseases, it is the intention of the writers to group the material (of over 200 pituitary cases) now at hand for description and analysis, according to the *anatomico-physiological classification* given in Table 1 following:

TABLE 1.—CLASSIFICATION—DISORDERS OF THE PITUITARY GLAND

I. Anterior Lobe	
A. **Hypo**activity	
1. **Pre**adolescent a. Aneoplastic b. Neoplastic	**Lorrain-Levi type** (Case I)
2. **Post**adolescent a. Aneoplastic b. Neoplastic	**Amenorrhea, dysmenorrhea** (female). **Loss of libido; impotence,** etc. (male)—reacting to anterior lobe treatment. Posterior lobe signs absent (Cases II, III, IV, XVII, XVIII, XX).

B. **Hyperactivity**

1. **Preadolescent** a. Aneoplastic b. Neoplastic	**Gigantism.** Posterior lobe signs absent (Case XXIV).
2. **Postadolescent** a. Aneoplastic b. Neoplastic	**Acromegaly.** Posterior lobe signs absent (Case XXV).

II. **Posterior Lobe***

A. **Hypoactivity**

1. Pars Intermedia (?).	**Polyuria** (Bab). Reaction to pituitrin. Signs of anterior lobe and pars nervosa disorder absent (Case XXVI).
2. Pars Nervosa	Pituitary **obesity** (Decreased metabolism, increased sugar tolerance. Polyuria and signs of anterior lobe disorder absent).
B. **Hyperactivity**	Hypophyseal **glycosuria** (increased metabolism, decreased sugar tolerance. Polyuria and signs of anterior lobe disorder absent) (Case XXVII).

III. **Bilobar***

A. Anterior and Posterior Lobes

a. **Hypoactivity**	**Fröhlich's type** without, or with polyuria (Biedl) (Cases VII, VIII).
b. **Hyperactivity**	**Gigantism** or **acromegaly** with **increased** metabolism and **decreased** sugar tolerance. Adiposity absent.
c. **Heteroactivity**	
1. Anterior Lobe hyperactive Posterior Lobe hypoactive	**Gigantism** or **acromegaly** with **polyuria** (Case XXIX).
2. Anterior Lobe hypoactive Posterior Lobe hyperactive	**Genital aplasia, nanism, amenorrhea,** etc., with pituitary **glycosuria** (Increased metabolism; decreased sugar tolerance).

---

* (1) Pre- and (2) Postadolescent varieties and (*a*) Aneoplastic and (*b*) Neoplastic types are subdivisions under each activity (Hypo- and Hyper-) as given under I, Anterior Lobe.

This classification, based solely upon the "hormonic" signs of hypophyseal disease, groups the disorders of this gland into three divisions, dependent upon whether one or both of the lobes were involved: (I) anterior lobe disorders, in which this lobe alone was involved; (II) posterior lobe disorders, in which this lobe, without clinical evidence of anterior lobe dyscrasia, was affected; (III) bilobar disorders, in which abnormal function of both lobes could be demonstrated. Each lobar division is subdivided into the activities prevailing, the anterior and posterior lobe disorders into the states of: (A) hypoactivity and (B) hyperactivity; the bilobar group into the states of: (A) hypoactivity, (B) hyperactivity and (C) heteroactivity. The last named (heteroactivity) comprises mixed cases, in which there were opposite secretory states of the individual lobes, such as hyperactivity of the anterior lobe, combined with hypoactivity of the posterior lobe, and vice versa. These activities are redivided into: (1) pre-adolescent and (2) postadolescent varieties, dependent upon the age incidence of the abnormal secretory state. A final division is made of the age incidence, into (a) aneoplastic and (b) neoplastic varieties.

Under the pre-adolescent hypoactivity of the enterior lobe is grouped the Lorain-Levi type of pituitary insufficiency. This type has not yet received the distinction of a special group division. Others, besides Lorain and Levi (Meige, Allard, Rennie, Kumell, Falta, Bell), in fact, nearly all writers who have collected a series of cases, have described similar types, intimating that the types were due to simple and single insufficiency of the anterior lobe. These types are characterized by having a classical arrest of osseous growth, with complete aplasia of the genital system, without additional endocrine symptoms referable to the posterior lobe.

In the postadolescent hypopituitarism of the anterior lobe, the writer has grouped those female cases which have had some osseous changes indicative of early anterior lobe disorder, and which developed, after the age of maturity, amenorrhea, metrorrhagia, or dysmenorrhea, dissociated from any local or general disease, that reacted completely to substitution treatment of anterior lobe extracts. Male cases in which signs of posterior lobe disorder are absent, but in which there is simple decreased genital function, such as loss of libido and impotence, which react entirely to the substitution of anterior lobe substances, would be grouped in this division. Under the hyperactivities of this lobe are described the well-known clinical syndromes of gigantism and acromegaly. These differ from case illustrations ordinarily found in the literature, by having negative evidence of posterior lobe involvement, such as polyuria, adiposity, abnormalities of basal metabolism, carbohydrate tolerance and unstriped muscle contractions.

Under the posterior lobe dyscrasias, the differentiation between the opposite states of activity is not so clear-cut. There is yet considerable uncertainty as to whether hypophyseal polyuria should be classified with the varieties of insufficiency or of overactivity of this lobe. These cases are most easily explained by Bab's theory, which attributes them to the pars intermedia insufficiency. The writers have observed 9 (of 11) cases of typical diabetes insipidus, reacting positively to hypophyseal extract treatment, 3 of which were free from other "hormonic" signs both of the anterior lobe and the pars nervosa disorders. This might be explained by defining a simple pars nervosa syndrome as consisting clinically, in the hypoactive state, of obesity, and, in the hyperactive state, of increased basal metabolism and decreased sugar tolerance. On the contrary, it is true that the majority of the polyurias attributed to the hypophysis have other endocrine symptomatology connecting them with either the anterior lobe or the pars nervosa portion of the posterior lobe. The hypoactivity of the pars nervosa, independent of the pars intermedia, is given as pure pituitary obesity, not associated with "hormonic" signs of the anterior lobe or polyuria, but having positive evidence of a decreased basal metabolism and increased sugar tolerance. Under the hyperactive varieties of the posterior lobe is classed hypophyseal glycosuria. This is a glycosuria which can be differentiated from one due to pancreatic disorder or one associated with ductless gland dyscrasia. It has the usual increased metabolism and decreased sugar tolerance, but is free from polyuria and "hormonic" signs of anterior lobe disorder.

Under the bilobar divisions are grouped those cases in which there is a concomitant anterior and posterior lobe disorder existing in the same individual. In order to include all cases thus represented, three activities must be considered: (1) hypoactivity of both lobes; (2) hyperactivity of both lobes and (3) heteroactivity, in which the lobes have an opposite secretory function. Under hypoactivity is classed Fröhlich's disease, either with or without polyuria (the former as described by Biedl). Under hyperactivity, those cases of gigantism or acromegaly and glycosuria, with which are associated increased metabolism and decreased sugar tolerance, without adiposity, are grouped. This classification takes many of the cases of both gigantism and acromegaly out of the simple anterior lobe dyscrasia variety, for it has been well known for many years that a large percentage of these cases have been associated with posterior lobe symptoms, such as polyuria, glycosuria, and disturbance of metabolism and sugar tolerance. Nevertheless, they have been classed by many authors either as simple anterior lobe dyscrasias, or have been grouped under the gross term "pituitary dystrophy."

The heteroactive varieties of bilobar pituitarisms should contain those cases in which the individual lobes of the hypophysis have opposite activities. For instance, gigantism or acromegaly, associated with polyuria, a not infrequent variety, should naturally be placed in this bilobar variety. Another considerable percentage of these diseases shows evidence of anterior lobe hyposecretion (such as genital aplasia and infantilism, amenorrhea, sexual impotence, muscle fatigue, and mental apathy), associated with posterior lobe hyperactivity (such as pituitary glycosuria, with increased metabolism and decreased sugar tolerance). It is the hope of the writers that this conception of a heteroactive bilobar division will be the means of disentangling many of the so-called dyspituitarisms and dystrophies, which have been so ill-defined that they add only confusion to the efforts toward diagnosis and treatment.

Clinical Types.—It was noted by the writers on grouping their cases, depending upon the age at which the individual lobe of the pituitary gland was involved and the state of activity of this lobe at the time of observation, that a great majority of *each group of cases presented a constant cardinal sign or symptom* which was the chief complaint for which the patient sought relief. To illustrate: In primary pre-adolescent anterior lobe hypopituitarism, the patient complained chiefly of amenorrhea. Those with pure anterior lobe insufficiencies occurring at or after adolescence, sought relief principally from metrorrhagia or dysmenorrhea. The early bilobar cases were affected chiefly with obesity. Cases occurring at about the age of adolescence had for their most distressing symptom a severe abdominal pain. In those occurring late in adult life there were a great number of constitutional symptoms, such as headaches, visual disturbances, syncopal attacks, nausea and vomiting, constipation, lumbago, and psychoneurotic manifestations. Among the purely nervous complaints, headache was the one that recurred most frequently, and a considerable number of patients presented themselves with the symptom of frequent, recurring periodical hemicrania as the most distressing complaint. Over 12 per cent. applied for treatment for epileptiform attacks. Extreme somnolence or hibernation and nocturnal insomnia are associated with nearly all the advanced late bilobar varieties.

To emphasize the relation of these various clinical manifestations to pituitarism, and in this way stimulate interest in the diagnoses and possibly the treatment of the secretory disturbances of this gland, rather than to add to the already superfluous clinical nomenclature of diseases of the pituitary gland, the writers have been led to designate as *clinical pituitary diseases* the pituitarisms with these striking presenting signs or symptoms. This clinical grouping of these diseases, it must be borne in mind, has no relation to the anatomico-physiological classification given above, although it will be found that certain clinical types are more frequently grouped under definite functional disturbances of a single lobe or both lobes of the pituitary. These clinical types, which will later be used in Part I under Hypopituitarism as descriptive group pictures, have been given the following names: (1) *pituitary amenorrhea;* (2) *pituitary metrorrhagia;* (3) *pituitary dysmenorrhea;* (4) *pituitary tumor;* (5) *pituitary obesity;* (6) *pituitarism with marked abdominal pain;* (7) *pituitarism with marked constitutional symptoms;* (8) *pituitary headache;* (9) *pituitary epilepsy;* (10) *pituitary somnolence or hibernation.* In Part II, the clinical types used as a means of grouping under *hyper*pituitarism are as follows: *gigantism, acromegaly, pituitary polyuria, pituitary glycosuria,* etc.

PART I

HYPOPITUITARISM

(Hypophysopathies)

Pituitary amenorrhea, p. 347—Pituitary metrorrhagia, p. 371—Pituitary dysmenorrhea, p. 385—Pituitary tumor, pre-adolescent, p. 405—Pituitary tumor, postadolescent, p. 420—Pituitary obesity, p. 445—Pituitary headache, p. 485—Pituitarism with marked abdominal pain, p. 497—Pituitarism with marked constitutional symptoms, p. 523—Pituitary epilepsy, p. 553—Pituitary somnolence, or hibernation, p. 587.

SECTION 1

PITUITARY AMENORRHEA

(Anterior Lobe Insufficiency of the Pre-adolescent, Aneoplastic Type)

Etiology.—The only important infectious disease with which this type has been associated is lues. This, as well as those insufficiencies of the pituitary occurring late in life, is sometimes associated with hereditary syphilis. This one possible removable cause should be borne in mind in every case, and the therapeutic test for this disease should be exhibited, even in the presence of negative physical or serological evidence. It is true that other racial tendencies probably have some bearing. Individuals with pituitarism undoubtedly recur in the same family, and are among the most important factors in making up the family physiognomy. Tumors, new growths, etc., are rather rare etiological factors in this early type. When they do occur, they are more likely to produce an early hyperpituitarism, which, on account of the growth and destruction of the pituitary gland, later produces a secondary hypopituitarism.

Symptomatology.—The patient, with *anterior lobe pituitary insufficiency, without pituitary tumor,* described below, came under observation eight years ago (January, 1910) at the age of twenty-seven, while suffering from an acute tonsillitis. At that time her skeletal development induced the inquiry into her menstrual history, which revealed many years of *continuous complete amenorrhea.* The summary history and other evidences of hypopituitarism to date are as follows:

History: Case I.—Mrs. E. W., aged thirty-five, housewife, American, first observation, January, 1910.

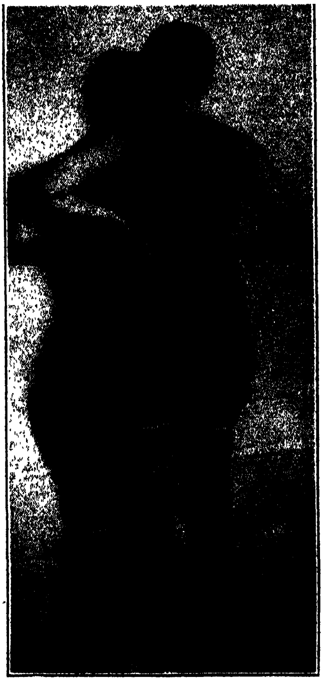
Present.—With the exception of the *absence of the menses* and concomitant secondary sexual characteristics, the normal period of adolescence, between the ages of twelve and fifteen, was free from infections, climatic influence, shock, or other known conditions which might influence maturity. On account of her apparently normal condition, no attempt was made to induce menstruation until the age of fifteen. At that time she began to consult physicians, who, during the succeeding four years, gave her various ineffective treatments consisting of iron tonics, alteratives, sitz-baths, suprapubic cuppings, vaginal tampons, dilatations of the cervix, and numerous uterine curettements. No impairment of the general health, abnormal configuration of the body, *localized deposition of fat,* or vicarious menstruations occurred up to the time of her marriage at nineteen. Marital intercourse produced no change upon her amenorrhea. Since her marriage, the patient claims to have had definite sexual desires, and sexual intercourse has been carried out with some pleasure, but without orgasm. The patient continued in the same amenorrheic condition until about the age of thirty-three. At that time there was a very slight menstrual flow, occurring every eight or nine months. This was not sufficient to require the wearing of menstrual pads, and the duration was less than twenty-four hours. During this entire time there have been no marked changes in the stature, height, posture, or *deposition of fat.* No other complaints, beyond a few intercurrent diseases, such as tonsillitis and mild bronchitis, and a few insignificant injuries, were present during the twenty-two-year course since the age of maturity.

Personal.—Habits simple, moderate coffee- and tea-drinker, no history of suspected venereal disease.

Family.—Mother living, well; father died of pneumonia at the age of forty-two. Three other members of the family. Two females, free from menstrual disturbances, abnormal growth or development, both short, stocky individuals, but not obese. One brother, well developed, of normal height and proportions. No family history suggestive of alcoholism, lues, or ductless gland dyscrasias, except possibly the stature of the father, a short, stocky individual.

EXAMINATION.—*General.* (*See* Figs. 1 and 2.)—Short, infantile type of woman, with girlish face; weight 127 pounds. Head small. Long bones not developed, hands and feet very small, but in proportion to the size and development of the remainder of the body. Measurements: Height, 5 feet 1 inch (155 cm.); circumference of head, 22 inches (59 cm.); chest, expiration, 31½ inches (80 cm.); forced inspiration, 34½ inches (88 cm.); at navel, 27 inches (69 cm.); at hips, 38 inches (97 cm.); length of humerus, 13 inches (33 cm.); forearm, 10 inches (25 cm.); from head to symphysis, 25 inches (64 cm.); from symphysis to soles of feet, 36 inches (91 cm.); length of femur, 21 inches (53 cm.); lower leg, 16½ inches (42 cm.); circumference of thigh, 18 inches (46 cm.); calf, 13 inches (33 cm.). *No abnormal distribution of fat:* absence of supraclavicular fat pads; mammæ small, plump, virgin in type; *no girdle obesity,* no fat about lower portion of the thorax posteriorly, or deposits in the abdominal wall, very slight fullness about the hips down to the middle of the femur, no deposition of fat above the mons. Very slight chloasma pigmentation about the forehead and the angles of the jaw, no other pigmentation about the body, no skin lesions or scars. Abnormal distribution of hair absent: lips and temporal regions anterior to the ears free from lanugo; eyebrows and eyelashes normal in amount and character of hair; slight amount of fine hair in axillæ, upper pubic hairline very straight and clear-cut; absence of hair on the chest, abdomen, or extremities. No cyanosis, edema, or dyspnea. No abnormal gait or posture; very erect, even with very slight tendency to lordosis. Pulse, slow, regular, equal, symmetrical, low volume and tension, no special type. Blood-pressure, systolic 126, diastolic 108. Temperature 98.6° F. (37° C.), respiration 18. Temperament phlegmatic.

CASE I. FIG. 1.—NOTE SHORT STATURE, SHORT LONG BONES, VIRGIN MAMMÆ, ABSENCE OF AXILLARY HAIR, AND OF GIRDLE OBESITY.



CASE I. FIG. 2.—POSTERIOR VIEW. NOTE SMALL HAND, SHORT BONES OF ARM, AND ABSENCE OF GIRDLE OBESITY.

Regional.—*Head:* Small, but well proportioned to the rest of the body; hair long, dry, of medium texture, well distributed, no alopecia. No compression symptoms in the head, no tenderness over sinuses, muscle insertions, or nerve exits. *Ears:* Air and bone conduction normal; Rinné's test negative; external ears well formed. *Eyes:* Pupils concentric, equal, react to light and accommodation; eye-muscles intact, no lagophthalmos, no nystagmus, no abnormal protrusion or increased intra-ocular tension; slight brownish pigmentation of both lids, sclera free from pigment. *Nose:* Straight, slightly flattened at the tip, not large or small compared with the rest of the face or head. *Mouth:* Palate arch high; teeth straight, regular, in perfect occlusion, no evidence of early decay; gums normal; mucous membranes of normal color, free from pigment. *Neck:* Thyroid not enlarged; no marked venous or arterial pulsation; lymph-glands not palpable. *Chest:* Well formed, expansion good, equal; tactile fremitus normal; percussion note resonant throughout; normal transmission of voice and breath sounds, no râles, rubs, or other adventitious sounds. *Heart:* Normal in size and shape, apex-beat not heaving; precordial area free from murmurs, rubs, and other abnormalities. *Abdomen:* Not distended or retracted, symmetrical, free from tumefaction, increased resistance, rigidity, tenderness, and dullness. *Spleen and liver:* Not enlarged to percussion or palpation. *Gall-bladder region:* Free from tenderness and tumefaction. *Kidneys* not palpable. *Stomach:* Tumefaction, visible peristalsis, and splashing sound negative. *Colon:* Not tender or palpable. *Vaginal examination:* Vulva normally developed, *os cervix finger-tip* in size; *uterus small, infantile in type,* freely mobile; tubes and ovaries not palpable, no masses or infiltrations in fornices. *Rectum:* No enlargement of hemorrhoidal veins, no abnormalities palpable in mucous membranes. *Extremities:* Joints and bones normal, with the exception of the small hands and feet and the short long bones; no edemas or varicosities. *Reflexes:* Babinski, Chaddock, Gordon, Oppenheim, negative; Achilles, patellars, present, equal; abdominals, pectorals, forearm, radio-ulnar, biceps, triceps, all present, equal; jaw-jerk present, Chvostek negative. *Lymphatic system:* Superficial glands not palpable.

LABORATORY EXAMINATION:

Blood:

Erythrocytes	4,800,000
Leukocytes	6,200

Wassermann: Negative.

Stained smear: Red-cells well stained, no marked variation in size; malaria plasmodia and other parasites negative.

Differential count:

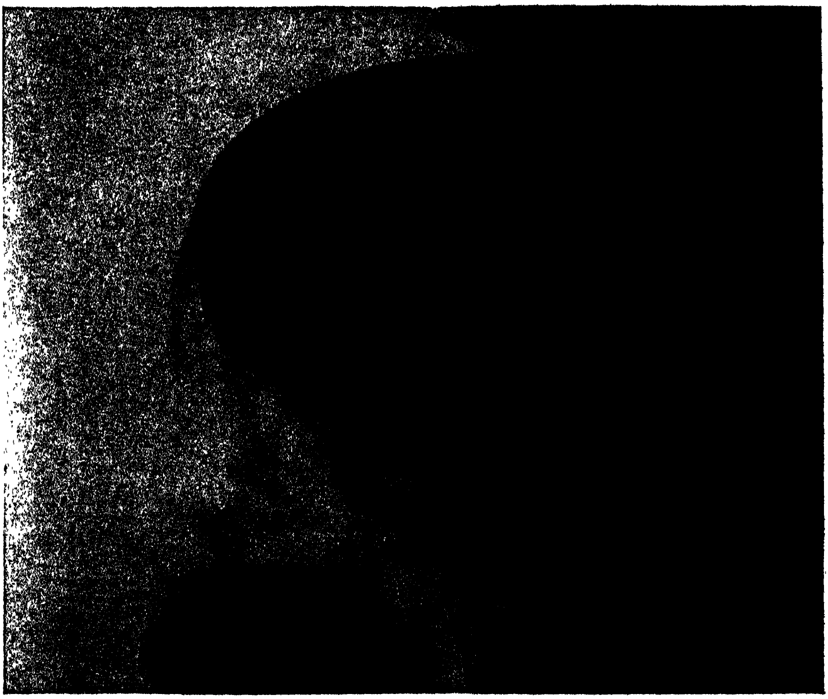
Polynuclears	73	per cent.
Small lymphocytes	19	" "
Large lymphocytes	4	" "
Transitionals	3	" "
Eosinophils	1	" "

Urine.—Single and twenty-four-hour specimens. Dextrose, albumin, casts, erythrocytes, and leukocytes negative.

Feces.—Parasites and occult blood negative.

SPECIAL EXAMINATIONS.—*Roentgenogram of Head.*—Skull not usually or unevenly thick. Sinus shadows small, free from opacities. *Sella* *turcica decreased in size* in comparison with the size of the skull. *Distance from the anterior to the posterior clinoid process only 2 mm.* No marked changes in the details at the base of the skull or in the sphenoid bone; mastoid cells free from opacities. (*See* Fig. 3.)

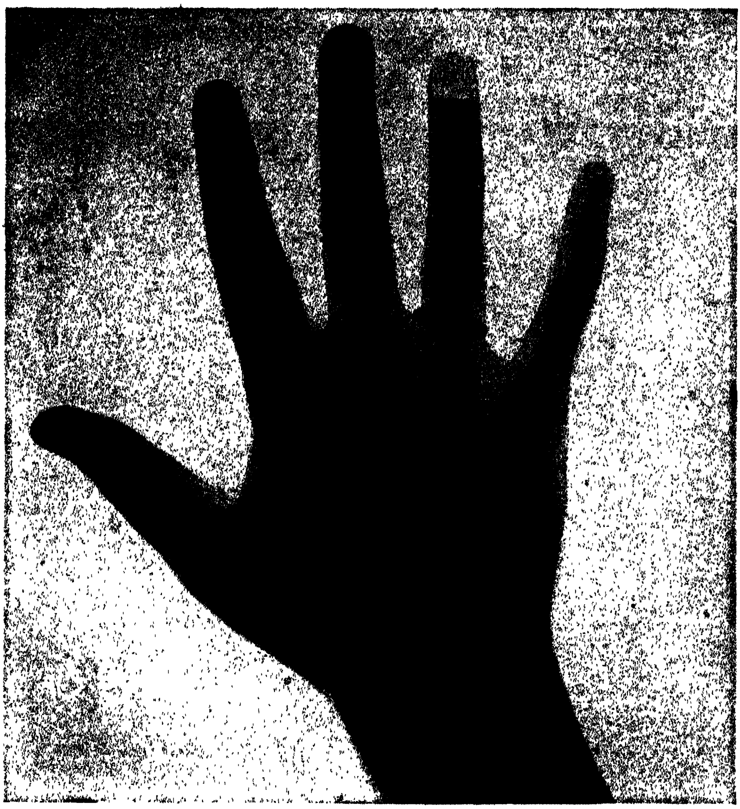
Roentgenogram of Hands.—Carpal bones all completely ossified. Epiphyseal ends of the phalanges and the metaphalanges united. *Absence of tuberosities* or *tufting* of the terminal phalanges. Shafts of phalanges *slender*. (Fig. 4.)



CASE I. FIG. 3.—NOTE PRACTICALLY NORMALLY-SIZED SELLA TURCICA, WITH CLOSE APPROXIMATION OF ANTERIOR AND POSTERIOR CLINOID PROCESSES, AND SLIGHTLY DECREASED DENSITY OF SKULL BONES.

Eye Examination.—No changes in color fields or perimeter marking. No errors of refraction or abnormal fundus changes.

Diagnosis: *Hypopituitarism, Anterior Lobe Insufficiency* (*without Involvement of the Posterior Lobe*), *Pre-adolescent Variety, Aneoplastic Type.*—The diagnosis of anterior lobe insufficiency of the pituitary gland in this case is based upon (1) the physical signs of a marked retardation and arrest in growth of the entire skeleton, and (2) the complete aplasia and absence of function of the gonads. The clinical proofs, excluding the posterior lobe from participation in this insufficiency, are the negative physical signs for girdle obesity and abnormal disturbances of metabolism, blood-pressure, temperature, pulse-rate, and involuntary muscle contractions. The fact that there is no enlargement of the sella turcica or evidence of intracranial pressure disturbances groups this case with the aneoplastic types. In order to have the diagnostic points presented by this case well grounded, it becomes necessary to take up the functions of the anterior lobe of the hypophysis. The secretion of this lobe of the pituitary gland has for its function the stimulation of the development of two systems, the osseous and the genital. While it is true that this secretion has been credited with hormonic influence on other organs and functions, it is principally its effects on the skeleton and the gonads which present the most decided clinical manifestations applying to diagnosis. The *specific* physical, histopathological, or chemical *changes of other organs, tissues, or functions* (such as metabolism) *produced by the secretion of any endocrine gland,* will be *defined* in these chapters *as hormonic signs* of that ductless gland. In illustration, the hormonic signs of the anterior lobe of the pituitary body are those specific changes of



Case I. Fig. 4.—Note Small Hand, Fragile Metacarpal and Phalangeal Bones, with Decreased Density, and Tapering Terminal Phalanges, without Mushrooming or Tufting.

growth and function of the skeleton and the testicles or the ovaries due to an abnormal secretion of this lobe of the hypophysis.

The striking overgrowth of the skeleton or some of the bones, resulting from an *oversecretion* of the anterior lobe of the hypophysis, as seen in acromegaly and gigantism, has been recognized since their first description by Minkowski in 1887, and by Marie in 1888. These bony changes, associated with definite enlargement of the pituitary gland, as demonstrated by an enlarged sella turcica, roentgenologically, and pituitary neighborhood intracranial pressure symptoms, were considered essential to diagnosis of diseases of the pituitary until 1901. At that time Fröhlich described "tumor of the hypophysis without acromegaly," directing attention to the fact that *disease of the pituitary gland was not always associated with osseous overgrowth of the maxilla and the hands.* Arnold, in 1894, and Porfick, in 1899, reported cases of acromegaly with *normal* pituitary glands, macroscopically and histologically: the earliest references to the fact that *tumor of the hypophysis or an enlargement of the sella turcica is not an essential to the diagnosis of pituitarism.* In 1906, and later in 1908, M. Bartels reported cases of dystrophia adiposogenitalia, which added to the picture of pituitary disease the two important signs of *adiposity* and *hypoplasia of the genitalia.* In 1910, Cushing published his monograph on "The Pituitary Body and Its Disorders," reporting a personal observation of over 40 positive cases, reclassifying the diseases of this body upon the clinical basis of focal and systemic signs of pituitary disease occurring alone or associated with clinical manifestation of other endocrinous dyscrasias. Biedl's volume on "Internal Secretions," in 1910, includes a wonderful review of the physiology and the experimental research done on these glands. Falta and Myers' "Diseases of the Ductless Glands," in 1915, has given a remarkably clear physiological and clinical exposition of diseases of the pituitary gland, based upon previous classification, *considering the entire gland as one organ.* Up to the present time, in the order of their importance, the cardinal factors for diagnosis have been as follows: (1) changes in the size of the pituitary gland, based on sellar deformity and intracranial pressure symptoms; (2) marked osseous overgrowth; (3) very decided obesity, with disturbance in the carbohydrate metabolism; (4) hypoplasia of the genitalia. Unless there was a combination of three or more of these cardinal signs present in the individual case, few diagnosticians had courage sufficient to attribute the patient's complaints to disease of the hypophysis. There has been no attempt made either to separate the pituitary into its two lobes or to group the signs and symptoms due to an overactivity or an inactivity of each separate lobe of this gland. The consequence has been that the divers varieties of kaleidoscopic syndromes, produced by the varying degrees and states of activity of a single or of both lobes, of neoplastic or aneoplastic types occurring at different ages, have made the diagnosis of these diseases decidedly confusing and complex. The purpose of the authors is to attempt to simplify the diagnosis of disease of this gland, first, by

TABLE 2. HORMONIC SIGNS OF THE

HYPOPITUITARISM

	Preadolescent	Postadolescent
A. **Osseous**	A. **Undergrowth. All bones. Lorain-Levi type**	A. **Undergrowth. Short and flat bones only. (Normal long bones)**
(a) **Measurements**		
	1. Short	1. Tall, or normal
	(a) Torso greater than lower. Span less than height	(a) Varies. Torso greater than lower or less than lower (eunuchoid)
1. Stature		
2. Head	2. Small	2. Small
(a) Sinuses	(a) Small	(a) Small
(b) Nose	(b) Pointed, straight	(b) Pointed, straight
(c) Superior Maxilla	(c) Normal	(c) Normal
(d) Chin	(d) Pointed, sharp	(d) Pointed, sharp
(e) Sella Turcica (X-ray)	(e) Small, except neoplastic type enlarged	(e) Small, except neoplastic type enlarged
3. Hands	3. Type "en petit," one-third smaller than normal	3. Small
(a) Phalanges (X-ray)	(a) Narrow, tapering, tuberosities and tufting absent	(a) Narrow, tapering, tuberosities and tufting absent
4. Pelvis	4. Broad, feminine type	4. Broad, feminine type
(a) Genu	(a) Valgum	(b) Valgum
B. **Genital**	B.	B.
1. Gonads (ovary or testicle)	1. Infantile	1. Normal
2. Uterus	2. Infantile	2. Normal
3. Menses	3. Amenorrhea, metrorrhagia, and dysmenorrhea	3. Tendency to dysmenorrhea, amenorrhea, and metrorrhagia
4. Sterility and impotence	4. Present	4. Present
5. Secondary Sex Characters	5. Absent	5. Present
C. **Muscular**	C. Proportionate to development	C. Normal
1. Muscle Tonus	1. Normal	1. Fatiguability frequent
D. **Mental**	D. Usually deficient or retarded	D. Average
E. **Dermal**		
(a) Teeth	(a) Upper incisors enlarged, lateral occlusion good	(a) Occasional separation and frequent enlargement of upper incisors
(b) Hair Distribution	(b) Absent	(b) Normal
F. **Temperature**	F. Subnormal	F. Subnormal
G. **Pulse**	G. Slow	G. Slow
H. **Blood-pressure**	H. Hypotension, or normal	H. Hypotension, or normal

HYPERPITUITARISM	
Preadolescent	**Postadolescent**
A. Overgrowth of all bones Normal giant Eunuchoid giant Acromegalic giant } Gigantism 1. Abnormally tall (a) Normal giant: torso = lower, span = height Eunuchoid giant: torso less than lower, span greater than height Acromegalic giant: torso greater than lower, span less than height	A. Overgrowth. Acral, short and flat bones only. (Long bones short) Acromegaly 1. Short and stocky, or normal (a) Acromegaly: torso greater than lower, span less than height
2. Large (a) Large (b) Pointed normal (eunuchoid giant) Blunt (acromegalic giant) (c) Normal, except prominent in acromegalic giant (d) Pointed, except prognathism in acromegalic giant (e) Normal, except neoplastic type enlarged	2. Large (a) Large (b) Blunt, rounded (c) Prominent (d) Rounded, blunt. Prognathism (e) Normal, except neoplastic type enlarged
3. Type "en longe," one-third larger than normal. No disproportion	3. Type "en large," spade hand, wrist wide, fingers broad and clubbed Infiltration of soft tissues over bones. Hands and head involved
(a) Wide, dense, tuberosities large, terminal tufting, exostoses	(a) Wide, dense, tuberosities large, terminal tufting, exostoses
4. Narrow, masculine type (a) Varum	4. Narrow, masculine type (a) Varum
B. 1. Large, well developed	B. 1. Large, well developed
2. Normal	2. Normal
3. Normal	3. Normal
4. Absent (present in a few years with transition to hypoactivity)	4. Absent (present after many years with transition to hypoactivity)
5. Present (even after hypoactivity occurs)	5. Present (even after hypoactivity occurs)
C. Normal, or overdeveloped 1. Loss (after few years' overactivity)	C. Overdeveloped 1. Retained after age of 40-45
D. Apathetic (after activity changes)	D. Abnormally developed, temperamental, loquacious, unstable
(a) Enlarged and separated upper incisors. Lowers separated in acromegalic giant (b) Increase on torso	(a) Separation of upper incisors constantly; frequently of lower, with prognathism (b) Marked increase on extremities and chest
F. Normal	F. Normal
G. Normal	G. Normal
H. Normal. Hypotension after change to hypoactivity	H. Normal, or above normal

separating it into its individual lobes, the anterior and the posterior, and, second, by defining as nearly as possible the disturbances due to (*a*) decreased secretion of each of these lobes, (*b*) increased secretion of each of the lobes, (*c*) differences in *a* and *b* occurring at various ages, and (*d*) differences of the types with and without pituitary tumor. It is necessary to understand that a large percentage of diseases of the hypophysis are not due to the changes in this gland which modify its size, shape, or form. It is true that there is a certain percentage of these diseases, of neoplastic etiology, which do increase the size of the gland, and consequently the size of the sella turcica, as well as produce pressure symptoms in its neighborhood. That this percentage is comparatively small is illustrated by the writers' personal statistics, showing that, of 200 odd cases of hypopituitarism, only 6 per cent. were associated with pituitary tumor. It is also essential to know that the types of oversecretion or of undersecretion of the lobes of this gland produce decidedly different changes in other organs and in the functions of the body. A better understanding of the functions of each lobe of the pituitary, and of the marked changes in the hormonic signs produced by the different secretory disturbances of each lobe, will certainly add materially to the ease of diagnosis, and hence the prognostication of the course and the application of the proper treatment in diseases of this gland.

With this point in view, the writers have reported herewith a simple case of primary insufficiency of the anterior lobe of the hypophysis, occurring before maturity, as the initial case, in illustrating the decided hormonic changes due to an almost complete absence of the secretion of this single lobe of the hypophysis. Before going into the detailed diagnosis of this case, it is thought advisable to separate the hormonic signs of hyper- and hyposecretion of the anterior lobe, and contrast the detailed effects of these opposite secretory disturbances on the organs and functions of the two systems (osseous and genital) whose development it to a large extent controls. To this have been added the hormonic signs of the dermal, muscular and nervous systems: the temperature and the pulse, which are markedly changed, but not absolutely specific, as these signs also occur in other endocrine dyscrasias.

As will be seen from Table 2, the *major hormonic signs of the anterior lobe* (A and B) are those referable to the growth and function of the *osseous* and *genital* systems, and the minor signs (C, D, E, F, G and H), to the dermal system, mentality, temperature, pulse and blood-pressure. The major signs attributed to the posterior lobe (I, II, III and IV) are those resulting in disturbed metabolism, deposition of adipose tissue, polyuria and unstriped muscle contraction. Associated with these are minor signs, affecting the secretion of other endocrine glands, the nervous system, temperature and pulse.

While it is true that the secretion from the anterior lobe seems to have a definite effect upon the development and function of the osseous and genital systems, it is acknowledged that other factors, endocrinous and endogenous, undoubtedly have considerable influence upon both the growth and the development of these two systems. Not all cases of retarded osseous growth and aplasia, for instance, can be attributed to hyposecretion of this lobe of the hypophysis. The French school (Brissaud, Meige, Bauer, Anton and Brammel) have many subdivisions of infantilism ("nanisme," "chétivisme," "nanisme complet"), many types of which have no relation to pituitary disorders. The above table contrasts the hormonic signs related to the anterior lobe in hypopituitarism with those of hyperpituitarism, and demonstrates the differences dependent upon the age at which this disturbed activity occurs (pre- and postadolescent). Attention is directed particularly to the extreme opposite change noted in the osseous system in pre-adolescent hypopituitarism (first column) as compared with pre-adolescent hyperpituitarism (third column).

The effect of the secretion from the anterior lobe upon the muscular tonus is a subject which has received comparatively little attention, but which has appeared to the writers to be almost as important as the difference present in the osseous growth and development. This is particularly striking when one compares the muscular development and tone of pre-adolescent hypopituitarism (Lorain-Levi type) with those of postadolescent hyperpituitarism (acromegaly). The extreme difference in the genital function and development is also emphasized in comparing the foregoing two types. In the first (Lorain-Levi type) the genitals are infantile and functionless, with the presence of sterility and impotence; whereas in the acromegalic, the genitals are unusually well developed and associated with hypersexuality. In pre-adolescent varieties of both over- and underactivity of this lobe, there is a tendency to decreased genital function. This is present as a cardinal sign in the hypopituitary postadolescent subject, and is soon acquired in pre-adolescent hyperpituitarism, on account of the early transition to inactivity in this variety. Decreased genital function and muscle tonus have occurred so constantly with hypoactivity of the anterior lobe, that they have established themselves as the best indicators of the state of activity of this lobe. Hence, the genital functions (menses, libido, and potency) and the muscular tonus (muscle fatigue or physical capacity), taken with the temperature, pulse, and blood-pressure, were considered, at the time of their determination, to be the significant signs of activity. The osseous changes, genital development, and secondary sex characters were interpreted as evidence of former activity which might have changed to the opposite state.

The intermittent enlargement and infiltration of local parts, such as the hands and face, in acromegaly, are undoubtedly due to changes in the soft tissue covering the short and flat bones involved, and are not a result of osseous change. The rapid changes in these localized swellings, besides the frequently associated sweating of these parts, helped to prove this origin. While there was no nervous syndrome specific of pituitary disorder, the different mental states, as described above, were most frequently demonstrable. The most significant mental change was probably that occurring in gigantism and acromegaly, with change of activity in this lobe. Change from a hypermental state to one of depression, apathy and indifference, if associated with loss of genital function and muscle tone, was considered particularly significant of transition to hypoactivity. The orthodontial markings in anterior lobe insufficiencies varied considerably. In the pre-adolescent hypopituitary individual, there was usually a tendency to overcrowding of the lower teeth, with fairly good lateral occlusion of the upper. The frontal incisors were constantly enlarged in those cases in which there was absence of genital function and development. The separation of the upper incisors occurred in postadolescent hypopituitarism, and was usually present in pre- and postadolescent hyperpituitarism, whereas the separation of the lower teeth was limited to the acromegalic giant and acromegaly, being absent in other hyperpituitarisms, as well as in all deficient secretions of the anterior lobe. The blood-pressure, temperature, and pulse were important signs of activity in this, as well as in other endocrine glands, but were by no means specific for pituitarism. Hence, they are valuable as signs of activity, but not as signs of any individual ductless gland. They are respectively subnormal and slow in the hypoactive cases, and normal or slightly above normal in the opposite state of secretion.

Basal metabolism determinations* have been made on only 32 of the cases which came under observation during the last six months. These cases have been grouped among the five varieties, so that there were too few in any one variety for satisfactory conclusions to be drawn.

The basal metabolism in these few cases of disorders of the anterior lobe of the hypophysis varied considerably. This is in contradiction to the theories previously advanced, to the effect that the anterior lobe secretion has no influence upon metabolism. One would believe that either there must be some relationship between the metabolism and the function of this lobe, or the clinical diagnosis excluding the posterior lobe of the hypophysis and the other endocrine glands, as an accompaniment in these cases, was incorrect. In the simple anterior lobe dyscrasias reported herewith, 7 cases had a basal metabolism varying from the normal. In 5 cases it was decreased, varying from

---

* Benedict's Portable Apparatus No. 19 was used for these determinations. The linear formula of D. Du Bois and E. F. Du Bois was used for computation of the area of body surface. The following table of Aub and E. F. Du Bois was taken as the normal standard for the calories per square meter of body surface per hour:

(Height-Weight Formula)

Age, Years	Males	Females
14-16	46.0	43.0
16-18	43.0	40.0
18-20	41.0	38.0
20-30	39.5	37.0
30-40	39.5	36.5
40-50	38.5	36.0
50-60	37.5	35.0
60-70	36.5	34.0
70-80	35.5	33.0

2 to 30 per cent., and in 2, it was increased 14 and 15 per cent. respectively. In one case in which anterior lobe extract was given therapeutically, the basal metabolism was increased from —30 to +8 per cent. during six weeks' treatment. This increase in metabolism to slightly above the normal was accompanied by relief of other symptoms, such as headaches, mental disability, muscular fatigue, loss of libido, etc. In the pure hyperactivities of the anterior lobe, the same discrepancy in basal metabolism determinations occurred. In the 4 cases in which the metabolism was determined, it was found to be normal in 2, and increased in 2. In 5 cases, originally diagnosed as simple anterior lobe hypoactivities, it was found that the basal metabolism was increased beyond 10 per cent., and the sugar tolerance markedly decreased, which necessitated a change in the diagnosis and grouping to the bilobar division, under the heteroactive variety.

The *carbohydrate tolerance** was estimated in 10 cases of anterior lobe dyscrasia. Of these, 7 were decreased, and 3 were increased in activity. Of the hypopituitarism cases, 5 showed an increased, and 2 a decreased, sugar tolerance; whereas, in the hyperactivities, 2 cases showed an increased, and 1 a decreased, tolerance. In the 2 cases having an increased basal metabolism, the sugar tolerance curve was normal.

The marked variation in those cases in which this decreased function of the anterior lobe occurs at different ages continues to be one of the most confusing clinical manifestations. In fact, that an insufficiency of the anterior lobe, for instance, occurring before maturity, produces an entirely different type of individual from that occurring during adult life, is not yet well appreciated. A detailed perusal of the hormonic signs referable to the insufficiency of the anterior lobe occurring before maturity (pre-adolescent variety) demonstrates that the undergrowth of the skeleton is an absolutely constant sign. This deficiency of the skeletal growth is not limited to the short, flat, or peaked (acral) bones; the long bones are also decidedly shortened. This absence of development of the long bones produces the typical short, stunted type of individual so characteristic of anterior lobe inactivity in childhood. In the cases in which there is withdrawal or marked diminution of this secretion early in life, there is constantly present a very small head, small hands and feet, in proportion to the other undeveloped parts of the body. The entire head is small, as will be shown by actual measurement of the circumferences. It is, however, well formed, in that its diameters are almost equal. The small head will consequently contain very small sinuses and a *very small sella turcica.* The face must necessarily be small, but it is always perfectly formed, all the features being properly placed to make it classical in outline and configuration. The facial features remain youthful throughout the entire life of the individual. These early anterior lobe hypopituitarisms are cases of ateliosis, or individuals of perpetual youth. This is due probably to the fact that there is complete arrest of bony growth and of development of secondary sexual characters. In normal individuals, the growth of the bones and other tissues of the face tends to keep the expression youthful as long as they are active, but as soon as retrogressive changes occur, the signs of age begin to appear. In these individuals there are no retrogressive changes, due to the absence of retrogression in the skeletal development of the head, as well as to arrest of gonad function. The nose is well formed, with a straight bridge and a pointed tip. The superior maxilla is broad and wide, producing a perfect upper toothline, with perfect lateral occlusion of the upper incisors. The chin is sharp and pointed, due to an anterior angulation of the inferior maxilla, causing tendency to overcrowding and consequent irregularity of the lower front teeth. *The sella turcica, except in those cases due to pituitary tumor, is usually smaller than normal.* This small sella turcica is probably due to the absence of the development of the bones of the head, and has the same relation to the head as the small sinuses, diameters, etc. *The hands* are the type *"en petit,"* one-third smaller than normal, and exactly *the opposite of those found in acromegaly.* They are exceedingly small and pudgy. The wrist is narrow and yet is wider in proportion to the length of the fingers than in the normal hand. This wide wrist compels the patient to wear a glove of almost the size worn by a normal individual of the same age, but the glove fingers are usually longer than the fingers of the hand. The fingers are very short and taper from the second phalangeal joints to the pointed tips. It will be noticed that the ends of the fingers are exactly opposite in form to those of acromegaly, which are broad, thick and clubbed. The nails are small, with absence of white crescents at the bases. The bones of the fingers are rather slender, with the presence, roentgenologically, of epiphyseal markings, but no tuberosities. This contrasts decidedly with the wide phalanges and the overgrown and tufted tuberosities of acromegaly. The long bones are underdeveloped. The measurements all show that they are decidedly shorter than those of the average individual of the same age, and the epiphyseal junctures are closed late. The pelvis is broad, feminine in type, and the legs tend to converge at the knees, producing the typical genu valgum.

---

* The sugar tolerance was estimated by the Janney-Isaacson method. The blood-sugar was estimated first after fifteen hours' fasting. Glucose, 1.59 grams per kilogram of body weight, was given, and blood-sugar estimations were again made, one hour and two hours following the ingestion of this amount. A normal curve was arbitrarily established, as follows: after fifteen hours' fasting, 0.10; after the first hour, 0.18; and after the second hour, 0.15. A decreased tolerance was considered one which would produce a higher curve during the two hours' estimations than the normal curve. Increased tolerance would show a curve 3 or 5 points below this curve.

In the *postadolescent variety* in which the deficiency of the anterior lobe of the pituitary occurs *after* the *epiphyseal ossification centers have been closed,* this lobe being normally active previous to the closure of these ossifying junctures, *the long bones are well developed and formed,* for the reason that they had already gone through their normal development and growth *before* this secretion was withdrawn. In the postadolescent case, there is, however, very marked *underdevelopment* in the head, hands, and feet, continuing into adult life, similar to the undergrowth of these structures in the pre-adolescent variety, which probably demonstrates that in the great majority of these cases there is partial insufficiency of the secretions of this gland before maturity. This retardation of the growth of the acral bones (bones of the head, hands, and feet) in adult cases, produces a more decided disproportion between these parts and the rest of the body—the long bones and the torso.

The *genital system* undergoes very decided changes, particularly in those cases occurring before puberty, such as the one reported herewith. The uterus, tubes, and ovaries remain infantile in size. In the complete inactivity of this lobe, there is an absolute amenorrhea, as was present in the case cited. Associated with this is the complete absence of secondary sex characters. The mammæ remain virgin in type, there is absence of axillary and mons hair, and marked decrease in the development of the external genital system and the mons veneris. In the less complete types of hyposecretion of the anterior lobe, occurring either before or after maturity, the genitalia undergo more or less imperfect development. In some cases the uterus and the ovaries are apparently normal in size, yet histological examination of the ovary shows a paucity of the graafian follicle development, with usually a marked undergrowth of the stroma of the ovary. The menses vary quite decidedly. The most frequent history is that of imperfect early menstrual disturbance, consisting of a *late maturity,* at the age of fifteen or sixteen. Usually the onset of imperfect menses is followed within a short time by a longer or shorter *interval of amenorrhea,* varying from a few months to a year, until there is complete absence of the periods. The periods then frequently return and occur at regular intervals, but the amount and duration of flow are usually very much decreased. Some cases give the history of *metrorrhagia,* with long intervals of amenorrhea between their prolonged periods. One case (II) to be reported in this series had periods in which there was a continuous small amount of flow for a number of weeks, sometimes for months, which was followed by a long interval of complete amenorrhea, varying from three to eight months at a time. *Dysmenorrhea* is usually a constant complaint in the postadolescent cases. Frigidity and sterility in the female, and loss of libido and impotence in the male, are nearly always present. The signs found in the female referable to the gonads are also present in the male. In those cases occurring before puberty, the testicles and the penis remain infantile, with absence of secondary sex characters. Impotence, with complete absence of sexual desire, is present in the postadolescent cases. Markedly decreased sexuality, with poorly developed genitalia, occurs in those cases developing in later adult life. In late adult cases, after the genitalia have already been well developed, there is sometimes a marked retrogression in the size of the genital organs, associated with a complete absence of libido.

In the *dermal system,* the teeth show very marked dedentition (absence of dentine), so that, while the teeth erupt at the proper age in the pre-adolescent case, they soon decay and "crumble." This is true of both the first and the permanent sets of teeth. It is not unusual to see marked decay of the permanent set of teeth as early as the age of fifteen or sixteen, as will be shown in a bilobar case (Case VII) in a subsequent report in this series. There is almost complete absence of hair on the thorax and the abdomen in these cases, and in the early preadolescent cases there is no hair on the face, and only very small amounts, or none at all, in the axilla and over the mons. In the postadolescent cases there is also complete absence of hair over the thorax, the abdomen, and the extremities. The hairline across the mons is very sharply horizontal, and only a small amount is present on the mons and in the axilla. The *temperature* in both pre- and postadolescent cases is subnormal, frequently ranging from 97° to 98.4° F. (36.1° to 36.8° C.). This subnormal temperature undoubtedly accounts for the chilly sensations and the amount of discomfort these patients experience on the slightest exposure. Cushing used this subnormal temperature as a diagnostic point, referring specifically to anterior lobe insufficiency, and was of the opinion that its restoration to normal by the injection of anterior lobe secretion hypodermically was a definite indication not only that the anterior lobe was involved, but also that there was an insufficiency in its secretion. This diagnostic procedure has not been confirmed by other authors. The writers are not inclined to believe that it has value, particularly in the primary unilobar insufficiency of the anterior lobe, or in those diseases of the pituitary gland in which both the lobes are involved. The fact that these cases have not been separated into the diseases of the individual lobes of the gland may be the cause of the difference in opinion with reference to the value of this thermic test. The *pulse,* in both age varieties of the insufficiency of the anterior lobe, is slow. This slow pulse, however, is not a specific sign of anterior lobe insufficiency of the pituitary, as it is found in other ductless gland insufficiencies, notably the thyroid, and is known, of course, as a sign in a great many other conditions. The hormonic signs of *hypersecretion* of this lobe of the hypophysis will be taken up in detail in the description of the second group of diseases of the pituitary gland, consisting of the hyperpituitarisms.

With this detailed description of the individual diagnostic signs of insufficiency of the anterior lobe of the hypophysis, it will be seen that the above case conforms definitely to an almost complete insufficiency of this lobe of the gland. That there was some secretion from the anterior lobe, of course, is certain, as life itself would not be compatible with an absolutely complete absence of function and secretion of this lobe. That this secretion, however, was at its minimum, must also be true, on account of the complete absence of the menses and the aplasia of the genitalia, coupled with complete arrest of the bony growth at the pre-adolescent age.

In order to avoid confusion regarding the diagnosis of involvement of the posterior lobe of the pituitary gland in this case, mention will merely be made that *there is no evidence of a disturbance of the secretion, either an overactivity or an inactivity, of this lobe* of the hypophysis. The diagnostic hormonic signs of this lobe relative to both its over-

and its under-function will be given in the section on Pituitary Tumor. Here it is necessary to say merely that the absence of girdle, mons, or mammary obesity, the negative evidence of disturbance of metabolism, such as carbohydrate tolerance, and the complete and prolonged freedom from such constitutional symptoms as headache, eye disturbances, nausea, vomiting, abdominal distention, dyspnea, polyuria, polyphagia, polydipsia, etc., prove conclusively that the posterior lobe was not involved in this case. The absence of a classical girdle obesity in this case is striking. It is the one cardinal sign missing from Fröhlich's syndrome of hypophyseal dystrophy. Rennie, Kumell, Bell, and Falta reported cases exactly similar to Case I, without, however, classifying them as pure anterior lobe insufficiencies. Personal investigation of the literature, with the point in view of discovering a good explanation for the absence of adiposity in these cases of pre-adolescent hypopituitarism, has failed to reveal a convincing explanation. While there is no local or hormonic evidence of the implication of the posterior lobe in this case, B. Fisher, Cushing, Falta, and others have ascribed the aplasia of the genitalia and the lack of the secondary sex development to the involvement of the posterior or nervous lobe of the pituitary. That this insufficiency of the gonads and the negative sex characteristics are really hormonic signs of the anterior instead of the posterior lobe of the hypophysis, is now conceded by Cushing as well as by many other investigators in this field. Nearly all authors are now agreed that the disturbance of osseous growth can be assigned to the anterior or so-called glandular lobe of this gland. It seems needless to add that the diagnosis of the aneoplastic variety is evident from the small sella turcica, and the absence of either general or pituitary neighborhood intracranial pressure symptoms.

Differential Diagnosis.—Other diseases producing an infantile or nanismic type of individual, marked arrest and retardation of the entire skeletal growth, and diseases affecting the normal development and functions of the gonads, must be considered in the differential diagnosis. Among these the most important are infantilism, cretinism, eunuchoidism, dwarfism, chondrodystrophy, and Mongolianism. In *true infantilism* there is an arrest of the growth *en masse* of all the organs and tissues—the child type. While the genitalia in nanism are undeveloped, the extreme degree of undergrowth is not present in these organs that occurs in this type of hypopituitarism. The mentality in infantilism is also very much reduced, whereas the mentality in these cases of hypopituitarism is practically normal, and sometimes much more advanced than in the average individual. The ossifying centers of the long bones in this type of pituitarism are usually open, roentgenographically indicated, at a later age than are those in infantilism. Hypopituitarism involving the anterior lobe is limited in its hormonic deficiencies to the skeleton and the gonad structures, whereas true infantilism should have marked evidence of deficiency of almost every structure, organ, and other endocrinous gland in the body. The etiology of true infantilism is frequently present. For instance, congenital syphilis, mitral stenosis, early tuberculosis, alcoholism, saturnism, or other chronic infections or intoxications which have a general effect on *all* the tissues of the body, can frequently be demonstrated. These etiological factors, with the exception of lues, typhoid, trauma, etc., which are common causes for secretory disturbances in the anterior lobe of the hypophysis, are usually absent in this type of pituitarism.

The *arrested growth of the cretin* can usually be easily differentiated from this pre-adolescent inactive type of anterior lobe hypophyseal disease. Other hormonic signs of myxinfantilism, such as the high saddle nose, the history of late dentition, and the consequent delayed eruption of the deciduous and the permanent teeth, the mental and the speech defects, the deafness, the pot-belly and the lordosis, the delayed locomotion, with the retardation of the ossifying centers, the dermal changes, and the effects of thyroid therapy, are diagnostic signs in cretinism which are absent in this type of hypopituitarism. The female cretins have the opposite type of menstrual disturbances to those of hypopituitarism. *Their menses occur very early,* at the age of eight or ten, and are usually very profuse in amount and prolonged in duration, lasting from four to six days. It is usually a few years after their occurrence that they begin to become irregular in interval, but even at that time the amount and duration are usually excessive instead of decreased. These characteristics of the menses contrast strikingly with the amenorrheas of the pre-adolescent hypopituitarisms involving the anterior lobe.

Eunuchoidism must be differentiated from this type of pituitarism on account of the similarity existing in the development and function of the gonads. The insufficiency of the gonads in eunuchoidism is due to a primary lesion in these organs, and is not the secondary effect caused by the withdrawal of the stimulating hormone produced by the anterior lobe of the hypophysis, as in the case of hypopituitarism. As proof that the anterior lobe of the pituitary gland is sufficient in its secretion in these cases of eunuchoidism, is the fact that the long bones are overdeveloped to an unusual length, a condition which could not be present if this secretion were decreased. This overgrowth of the long bones produces a classical type of individual, in which the two simple signs are an exceedingly long, slender, gracile eunuchoid hand, and an extreme difference in the measurement from the top of the head to the symphysis (upper measurement) as compared with that from the symphysis to the soles of the feet (lower measurement). The difference in these measurements merely represents the disproportion in growth between the long bones and the short bones. In the upper measurement, only the growth of the short bones is registered, while the lower measurement is due entirely to the length of the long bones included in this distance. In addition, the length of these long bones is due to the late closure of the epiphyseal junctures, which occurs in the primary insufficiency of the gonads. The contrast present in the length of the long bones, and also of the short bones of the fingers, is so decided as to be almost sufficient in itself to differentiate eunuchoidism from pre-adolescent anterior lobe insufficiency of the pituitary. The differentiation of a pure postadolescent anterior lobe insufficiency from a late eunuchoidism is, however, not so simple. In the postadolescent hypopituitarism, the long bones have already been fully developed, and consequently this sign is absent. In these cases, however, the peaked or acral bones of the face, the hands, and the feet have usually retained some of the characteristic undergrowth of hypopituitarism. This produces the typical small, pudgy hand, with tapering fingers, the small feet, and the small pituitary head as compared with the rest of the body —points which contrast very strikingly with the extremely long, slender, eunuchoid hand, the large feet, and the disproportioned head usually present in the cases of eunuchoidism. There is no decided evidence in the genitalia themselves upon which to differentiate these two conditions. Convincing evidence must be obtained from the difference in the development of the individual parts of the skeleton. The *different types of dwarfism* usually have sufficiently characteristic points referable to their individual types, identifying them with one of the varieties of the dwarfs. The Lilliputians, Paltauf's type, and the rachitic dwarfs, all have special characteristics identifying them with their individual types of dwarfism. While the genitalia in most of these cases are undeveloped, many of them have the normal function of these organs. The epiphyseal centers in a great majority of all dwarfs are closed much earlier and more permanently than are those of hypopituitarism. The rachitic dwarf has typical signs of rickets. None of these groups of cases has the perfect combination of arrested skeletal growth with late closure of the epiphyseal centers, associated with a complete lack of development and insufficiency of the function of the gonads.

Achondroplasia is very easily diagnosticated by the unusually long torso as compared with the short extremities. All the fingers are of the same length, the genitalia are well developed, and the roentgenograms of the cartilages and the epiphyseal ends of the bones are entirely different from those seen in the well-proportioned infantile type of stature of the pre-adolescent anterior lobe hypophysopath.

Mongolianism is easily separated from this type of hypopituitarism by the marked defect in the mentality and the absence of hypoplasia of the gonads.

Treatment.—In these cases of aneoplastic hyposecretion of the pituitary gland involving the anterior lobe alone, the treatment consists in (1) antiluetic, to remove a possible cause for the decreased function of the gland (*see* Etiology), (2) substitution glandular therapy, *i. e.*, anterior lobe extract hypodermically and anterior lobe substance given by mouth, and (3) treatment of other endocrinous dyscrasias, secondary lesions, and symptoms. **Specific treatment** is given as for any other syphilitic lesion. The **glandular treatment,** as has been stated above, is given both by mouth and hypodermically. **Extract of anterior lobe of pituitary** is given intramuscularly, minims xv (0.92 c.c.) at intervals of from one to four days. The glandular substance of this lobe is given in doses of grains 2½—15 (0.16—1.0 gram), after meals.

Substitution treatment for other endocrine insufficiencies, such as the ovarian inactivity existing in this case, should receive considerable attention. In fact, it has been the writers' routine method to attempt to overcome secondary glandular insufficiencies in the treatment of ductless gland diseases, before treating the primary glandular dyscrasia, that is, in these cases, to substitute the secretions from the ovary by giving **corpus luteum** by mouth, and this substance with "**ovarian substance**" hypodermically. This is done, first, with the purpose of confirming the diagnosis, and, second, to eliminate secondary endocrinous insufficiencies from the field, so as to observe the therapeutic effect of treatment directed toward the suspected primary cause of the hormonic disturbances. Any other ductless gland involved, as is more frequently the case in the postadolescent types both of the anterior and the posterior lobe insufficiencies, should demand treatment based on the indications present. For instance, secondary hypothyroidism, frequently associated with the cases occurring later in life, should be overcome by the usual treatment, given either before or with the treatment directed toward overcoming the ovarian insufficiency, and previous to the treatment of the anterior lobe of the pituitary itself. The writers will discuss this routine form of treatment considerably more in detail in later cases, where it has more definite application. Much information can be obtained from properly directed treatment, taking up one ductless gland at a time and carefully studying the effect of simple substitution of the secretion from this gland. For example, in Case I, even before ovarian or pituitary treatment is given, if the patient can be properly controlled, it would be well to observe for a considerable length of time the simple effect of **antiluetic treatment**, as this alone might be able to restore the secretion of the anterior lobe of the pituitary to its normal balance. In this case, **salvarsan** and **mixed treatment, iodids** and **mercury**, were given for a long time, without effect on either the amenorrhea or the arrested skeletal growth. Although there was no evidence, either in the blood serum or in the physical examination, to substantiate a possibly acquired or congenital lues, this treatment was given purely for diagnostic purposes. No opportunity was afforded to give glandular treatment, and consequently, the effect of this cannot be reported.

Prognosis.—In those pre-adolescent insufficiencies of the anterior lobe which are diagnosed early, the prognosis should be much better than it is at present. The forthcoming additional knowledge on ductless gland functions, and the simplification of the diagnosis so that this can be made at an age before maturity, with the better understanding of polyglandular therapy, offers some possibility for more favorable prognosis. *With regard to life*, it is more than likely that the simple anterior lobe insufficiencies, free from posterior lobar involvement, unless these cases are later complicated by neoplasm of the pituitary, run a comparatively prolonged and benign course. They certainly are much freer from constitutional disturbances, such as headaches, visual defects, dyspnea, abdominal symptoms, obesity, secondary infectious diseases, etc., than are those varieties which are associated with insufficiency of the posterior lobe. It is also true that simple anterior lobe insufficiencies are very much more favorable than simple posterior lobe diseases of either deficient or overactive secretion. The patient described, for instance, lived through a course of twenty-two years of insufficiency of secretion of the anterior lobe of the hypophysis, with absolutely no discomfort. The fact that her stature was short, and that she had had no periods, after a few years, practically gave her no concern. This is not true of the posterior lobe deficiencies. Such patients constantly complain of many decided constitutional disturbances, ranging almost from cranium to toes; besides which they seem to be exceedingly susceptible to other diseases. Consequently they are more or less incapacitated by the constitutional hormonic symptoms of the posterior lobe deficiency, associated with acute infections such as bronchitis, rhinitis, rheumatism, neuralgias, neuritis, nausea and vomiting, constipation, extreme nervous irritability, etc. It is true that the anterior lobe insufficiencies in some cases do develop more or less psychic disturbances. These are more marked in the adolescent or postadolescent cases, however, and are limited to a considerable extent, in the less complete type, to the premenstrual week. The ultimate exitus in these cases is usually due to some other disease, provided they do not develop a later pituitary neoplasm. In relation to neoplastic growths, it can also be said that the anterior lobe insufficiencies are not as liable to change into neoplasms as those disturbances beginning in the posterior lobe or in the infundibulum of the hypophysis.

Pathology.—The established functional pathology of both of these lobes has been proved by three methods: (1) the removal of one lobe or a portion of both lobes of the gland from animals; (2) the artificial introduction of this glandular substance into animals by injection or feeding experiments; (3) clinical observation of the effects of increased or decreased secretions of either one or both lobes of this gland, in control (operative or autopsy) cases. The most important of these are the following: (1) Paulesco, Cushing and his associates have proved that *complete removal or destruction of the pituitary is uniformly fatal.* In a few days there is tremor, fibrillary twitching, arching of the back, slowing of the pulse and of respiration, hypothermia, apathy, coma, and death—the so-called cachexia hypophyseopriva acuta. Bell claims that this is produced only after amputation of the infundibulum. (2) Cushing and his associates, Aschner and Biedl, have demonstrated that partial *hypophysectomy* (of both lobes) in animals (*see* Fig. 5) is followed by adiposity, increased carbohydrate tolerance, hypothermia, nutritional changes in the skin and its appendages, sexual inactivity and gonad hypoplasia, retardation of body growth, mental dullness, transient polyuria, and histological changes in other ductless glands. (3) *Partial removal* (experimental) or decreased secretion (clinical) of the *anterior lobe* of the pituitary produces (*a*) retardation of the growth of the bones, and (*b*) diminution of the development of the endocrine function of the gonads which are concerned in the development of the secondary sex characters.

The effects of artificial introduction of these glandular substances into animals, either by injection or feeding experiments, is reported by Aschner as follows:

"In comparison with the development in controls (A), *animals fed with whole gland extract,* in which the *anterior lobe* is the responsible factor, are larger, more muscular and edematous in appearance, indicating increased development and activity. Even at the early age of two and two-fifths months, from one to two months before normal sexual maturity, the ovary is matured and shows active ovulation and graafian follicle formation, relatively few primordial follicles, and some increase in the amount of interstitial tissue. This striking appearance in so young an animal gives the impression that an early ovarian maturity has been produced by the feeding of the pituitary extract. The fimbriated end of the tube is more branched and the lining columnar cells are more ciliated and indicate greater activity. There is marked hypoplasia of the uterine mucosa, the lining cells of which are uniformly ciliated and active, and there is abundant gland formation in the endometrium. The appearance presented by the latter strikingly resembles, in microscopical appearance, the hyperplastic endometrium of early pregnancy. There is generally increased vascularity produced in the whole sexual system. A somewhat similar change is produced by the feeding of corpus luteum to the female, but not the same degree as after anterior lobe administration. (B) *Intravenous injections of extracts of the whole gland* raise the blood-pressure, as demonstrated by Oliver and Schafer. These effects are due in reality to extract of the posterior lobe, or pars nervosa, as shown by Howell. The rise in blood-pressure is due to arteriospasm of all the vessels except the renal

CASE I. FIG. 5.—TWELVE MONTHS OLD HYPOPHYSECTOMIZED DOG (Left) AND CONTROL OF SAME LITTER (Right). (From Aschner.)

Operation was performed at eight weeks. In hypophysectomized dog, note marked osseous underdevelopment of long bones, obesity, somnolence, and genu valgum, in comparison with normal control.

arteries, which, after a brief period of constriction, dilate. This dilatation of the renal vessels, together with the specific stimulation of the renal epithelium, *gives rise to diuresis.* (This view has recently been contradicted as detailed in Part II, Section 13, on Pituitary Polyuria, page 641.) (6) The *active principle of posterior lobe extracts,* or so-called *infundibulin,* also stimulates contraction of the smooth muscles of the uterus, bladder, intestine, and dilator of the pupil, and tends to cause glycosuria, thus resembling closely in its effects the action of epinephrin, though the effects are not identical. Extracts of the pars nervosa exert a galactagogue effect. [This has been contradicted by later investigators.] (D) After prolonged *feeding of anterior lobe extract,* over a period of eight or nine months, the sexual instincts are early awakened, along with the early maturity of the sex gland. As a result of this, a pair of rats, after anterior lobe feeding over a number of months, bred earlier and oftener, the female of this pair having two pregnancies in seven months as compared with none in the female of the control pair. The effect of the anterior lobe feeding lasts throughout the adult life of the animal. The control rat never reaches the degree of development and activity shown by the animal receiving the anterior lobe extract; for even at the age of ten months, after eight and one-half months of anterior lobe feeding, the latter still shows a greater, more active and mature sexual development than the control. The feeding of pituitary anterior lobe to parent rats exerts its stimulating influence upon the offspring in the intra-uterine life and during lactation, and when the experiment is carried farther and the feeding to the young is continued after weaning, it has an even greater stimulating effect on growth, weight, and development, and causes earlier and more frequent breeding, and an increased number of offspring in the litters. The stimulating effect on the sex gland is greater the longer the influence of anterior lobe administration is exerted. (E) The *extract of pituitary posterior lobe,* even after prolonged administration, does not stimulate growth in general nor the development of the sex glands, as does anterior lobe even after a very short period. Thus, for example, there is a much less marked development of the sex glands after administration for two and one-half months. The *posterior lobe element in the whole gland extract has an undoubted retarding influence upon the development of the sex* glands, an effect very similar to that of ovarian extract on the testes. This is shown by the relatively incomplete development of the testes, for example, after eight and one-half months of posterior lobe feeding. If given in too large doses, the extract causes, in the rats, loss of weight, a mild enteritis, and *increased intestinal peristalsis.*"

Pathological change in this primary pre-adolescent anterior lobe hypopituitarism, in the gland itself, is said to be an aplasia of the anterior or glandular lobe of the hypophysis. The histology of the anterior lobe is so variable and changeable that no microscopic picture has been absolutely accepted as the fixed adult type of a normal lobe. There are many good descriptions of a hyperplasia of the anterior lobe of the hypophysis, for instance, as described by Erdheim and Stumme, during pregnancy, and that found in hyperplastic adenoma of the early acromegaly. While there is absolutely no unanimity of opinion regarding this histological picture, Benda and Dean Lewis maintain that there is multiplicity of the eosinophilic cells over the normal neutrophilic and basiphilic cells. Erdheim believes that it is necessary for these eosinophilic cells to be gathered in adenomatous clusters in order to indicate pathological hyperplasia. It is taken for granted that a decided paucity of these cells would be found in hypofunction and secretory disease of this lobe.

Too few a number of such cases have been examined, really, to determine the histological changes present in the gland. The pathological changes in other organs are insignificant, with the exception that in some cases there has been reported a hypoplasia of the aorta, formerly considered as a sign of chlorosis. The most important macroscopic finding is the complete aplasia of the genital tract. The uterus remains absolutely in the infantile state, the ovaries show no evidence of function, and the corpus luteum development is practically that of a child before maturity. The absence of marked changes in other organs is borne out by the negative clinical manifestations of either structural or functional changes in other ductless glands, so strikingly present in cases in which this gland becomes either completely or partially insufficient in postadolescent life. The osseous system probably undergoes slower ossification, and it would be important to give this condition more consideration in those bone diseases in which there is marked retardation of the ossifying centers before the age of maturity. The other endocrine organs, such as the suprarenal, the thymus, the thyroid, the parathyroid, and the pineal gland, have not been found decidedly changed in this type.

SECTION 2

PITUITARY METRORRHAGIA

(*Anterior Lobe Insufficiency of the Postadolescent, Aneoplastic Type*)

Etiology.—The etiology in the following case is very indefinite. The family history shows that the mother and the grandmother were typical infantile individuals. There is no definite trauma, infection, or other disease bearing on the changes in the pituitary secretion. The past history shows that the patient had measles, mumps, and chicken-pox. These occurred, however, many years previous to adolescence, and whether they were in any way related to the insufficiency of the anterior lobe secretions is very questionable. The sociological aspect of the early deficiency of the pituitary is important, as it relates both to marriage and to the function of childbearing of the individual. The marked frigidity and sterility present in these cases make them types of individuals who are less liable to marry on account of the lack of sexuality. After marriage, unless the condition is corrected by treatment, an absence of libido and conception is usually the rule. For this reason, if for no other, they demand more scrutinizing diagnosis and properly applied, intensive early treatment.

Symptomatology.—History: Case II.—Mrs. N. A., aged twenty-five, referred by Dr. Oscar Elbrecht, St. Louis, May 22, 1918, St. John's Hospital, General No. 2112.

Present.—Chief Complaints: (I) Menstrual disturbances, consisting of long periods of *metrorrhagia,* from two weeks to five months in duration, followed by long intervals of amenorrhea; (2) *dull pain in the right iliac region,* at times present posteriorly, and somewhat affected by position; (3) *sterility;* (4) occasional *frontal headache;* (5) attacks of *cardiac palpitation;* (6) *constipation;* (7) *emotional attacks.*

Duration.—Eleven years.

Course.—Onset.—The patient reached maturity at the age of fourteen. The first menses consisted of a *very profuse and prolonged flooding,* requiring medical attention. After two weeks of rest in bed, with vaginal packing, this period stopped. *Following this, there was complete absence of periods for three months,* when the patient had a recurrence of a very profuse menstrual flow.

Progress.—The *attacks of metrorrhagia, followed by months of complete amenorrhea,* have recurred since maturity. The average duration between the metrorrhagic periods was two or three months. At the age of sixteen a curettement was performed, stopping the flow entirely for one year. During this time the patient's general health was good, and was not associated with any local or constitutional symptoms. At the end of one year, an extreme metrorrhagic period again occurred, with the same characteristics as before. These periods would be profuse and would continue until relieved by treatment, such as curettement, vaginal and uterine packing, electrotherapy, etc. The flow never ceased spontaneously. At the age of eighteen, the patient was curetted for the second time. Following this curettement, she was again entirely free from periods for about one year. A third curettement was performed at the age of twenty, and the patient was free from periods for nine months. The fourth curettement was performed two years ago, at the age of twenty-three, following which the patient was free from menses for six months. After this six-month interval of amenorrhea, the periods again commenced, each lasting from five to seven days, recurring at intervals of twenty-eight days, for two or three successive months. There was then an interval of complete amenorrhea for six months. Following this, about one year ago, the patient was given hypodermic injections of corpus luteum, after which the periods reappeared. Menstrual flow has been more or less constant up to the present time, for the past six months, with intervals of freedom of two weeks on several occasions. There has not been a large amount of flow during this prolonged period of metrorrhagia, the flow requiring the wearing of not more than two menstrual pads a day. The patient has suffered from hot flushes, nervousness, and numbness of the hands during the premenstrual week ever since maturity. There has been *absolutely no abnormal deposition of adipose tissue or obesity of any type during her entire life.* The weight has always remained at about 100 pounds, except on one or two occasions following profuse bleeding and curettage. Following the curettement two years ago, a *dull, aching pain in the right iliac region* occurred, which has been present more or less constantly since that time. This pain is aggravated by moving quickly to the side or by twisting. At times it radiates through the body to the posterior portion of the pelvis. It is not associated with the act of micturition. *Constipation* has been present, even previous to maturity. The patient has been required to take mild cathartics, as long as she can remember. The pain in the right iliac region is occasionally exaggerated by bowel movement. This pain in the right iliac region, however, has not been definitely increased previous to the periods, or associated definitely with them, except in regard to the curettement, which it followed. *Emotional attacks* occur, consisting of *marked nervousness and irritability.* The patient at times becomes very much depressed and discouraged, and extremely sensitive about her general state of health. She worries considerably with each recurrence of her menstrual disturbances, and is particularly very much depressed concerning her *inability to conceive.* No signs or symptoms referable to other systems.

Past.—Measles, mumps, chicken-pox. Four curettements, no other operations, no injuries.

Personal.—Patient has been married six years, without conception.

Appetite fair, sleeps fairly well, disturbances of bowels and menses as noted above.

Family.—Father living, well. Mother died of cancer. Two sisters, one brother living. Immediate relatives of average size, with the exception of mother and grandmother, who, from description, were typical infantile types of individuals.

Examination.—*General.*—*Infantile stature,* short, slender, with *very small hands* (size of glove, No. 5½), wrist narrow, fingers slightly clubbed, crescents of nails not showing, feet very small (size of shoe, No. 2B). *Absence of abnormal adiposity in the girdle region, mons, or mammæ.* Very slight *chloasma pigment about the angles of the jaw and the mouth.* Fine lanugal hair anterior to the ears and on the upper lip. Pulse, slow, regular, equal, symmetrical, low volume and tension, no special type. No abnormal gait, station, or position. Veins visible in the neck, very slight pulsation of veins and arteries. Measurements: height, 5 feet 2 inches (157 cm.); from vertex of head to symphysis, 31 inches (78 cm.); from symphysis to soles of feet, 31 inches (78 cm.); length of humerus, 10½ inches (27 cm.); forearm, 9 inches (23 cm.); femur, 15 inches (38 cm.); lower leg, 15 inches (38 cm.); circumference of head, 21 inches (53 cm.); of neck, 11½ inches (29 cm.); of chest, 29 inches (74 cm.); at navel, 23 inches (58 cm.); at hips, 31 inches (78 cm.). Weight, 92 pounds. Pulse, 74-84. Temperature, 97.4°-98.4° F. (36.33°-36.88° C.). Respiration, 18-22.

Regional (Positive Physical Signs).—*Head,* small, girlish face; hair normal. Mouth, marked *spacing between the upper incisors and the canines,* all teeth hard, no loss of dentine, some overcrowding of the lower teeth; four small cavities have been present in the entire set of teeth. Neck, negative. Viscera of *thorax* and *abdomen,* normal. *Vaginal,* uterus of normal size, retroverted, slightly displaced to the right; slight fullness just to the right of the uterus, no marked pain or tenderness in either fornix.

Laboratory Findings.—*Urine.*—(*a*) Single specimen, milky in color, specific gravity 1.010, reaction alkaline. Moderate trace albumin, occasional leukocyte. Dextrose, erythrocytes and casts negative.

(*b*) Catheterized specimen, pale, specific gravity 1.002, faintly acid in reaction.. Albumin, dextrose, leukocytes, erythrocytes and casts negative.

(*c*) Twenty-four-hour specimen, 1,330 c.c., color straw, specific gravity 1.010, reaction acid. Albumin, dextrose, leukocytes, erythrocytes and casts negative.

Feces.—(*a*) Following blood-free diet, brown, semiformed. Mucus, pus, ova, parasites and occult blood negative.

(*b*) Second specimen, mucus, pus, ova, parasites and occult blood negative.

Blood:

Wassermann	negative
Erythrocytes	4,450,000

Leukocytes	4,400
Hemoglobin	90 per cent.
Stained smear	normal

Sugar Tolerance Test:

(5-23-18.) Blood-sugar	0.076
	(Normal, 0.10-0.120)
After taking 200 grams (7 ounces) dextrose in twenty-four hours, by mouth, with injection of 1/1000 adrenalin	0.114
(5-25-18—Janney-Isaacson method.) Following fourteen-hour fast	0.072
Two hours later, after taking 73.6 grams (2 2/3 ounces) dextrose	0.096

SPECIAL EXAMINATIONS.—*Fluoroscopic.—Head, neck, chest, stomach, and colon* normal.

Roentgenogram of Head.—Anterior-posterior diameter slightly increased. Nasal bone at an angle of about 30 degrees, extending one-third the distance to the tip of the nose. *Frontal sinus small. Sella turcica very small.* Other details normal.

Diagnosis: *Hypopituitarism, Postadolescent Variety, Anterior Lobe Involvement, Aneoplastic Type.*—The diagnosis of hypopituitarism in this case is made from the history of the duplex combination of almost complete arrest of skeletal growth with very decided menstrual disturbances. The physical signs implicating the pituitary as the cause of the patient's menstrual anomalies are those obtained from the skeletal development, indicating decided withdrawal of the growth hormone of the anterior lobe. The exceedingly small, well-proportioned, girlish face; the long, straight, pointed nose; the pointed chin; the separation of the upper teeth; the slight chloasma about the forehead and the mouth; the classical hands and feet, with the undergrowth of the long bones,—make up the pathogenic changes of pituitarism in the skeleton not simulated by any other disease. The coupling of this specific retardation of the osseous growth with decreased function of the ovaries, in the *absence of obesity and the presence of decreased sugar tolerance*, not only speaks for the diagnosis of *hypopituitarism*, but also proves rather conclusively that the anterior lobe of the pituitary gland is the one involved. *Negative clinical evidence of pelvic or other disease* to account for the metrorrhagia, associated with the long periods of amenorrhea, points convincingly to the anterior lobe of the pituitary as their source. The absence of girdle obesity, negative changes of metabolism, polyuria, cranial and other constitutional symptoms referable to vasomotor and blood pressure changes, prove that the posterior lobe has not been affected, either as to inactivity or as to overactivity. It will be noted from the case report that in both estimations of the tolerance for carbohydrates, there was quite a decrease of blood-sugar following the ingestion of dextrose, denoting a high or normal tolerance.

This is one of the most reliable tests of posterior lobe activity. Whenever the secretion from the posterior lobe becomes insufficient, the hyperglycemia, as estimated in the twenty-four hour or the two-hour test (Janney-Isaacson modification of Woodyatt method) has been found by the writers to decrease, instead of increase. The further diagnosis of this case as aneoplastic is based upon the small sella turcica and the absence of clinical signs of intracranial pressure in the neighborhood of the pituitary gland.

Differential Diagnosis.—The differential diagnosis in this case pertains mostly to other lesions of the adnexa and constitutional diseases which produce attacks of amenorrhea and metrorrhagia. A considerable number of these cases are treated for endometritis, fibroids, and local adnexal disease, such as cystic ovaries, or ovarian cysts, not only on account of their marked disturbances of menstrual flow, but also on account of the pain present in the lower part of the abdomen and pelvis. The adnexal diseases are usually easy to differentiate by the history and physical signs, with the exception possibly of retention corpus luteum cysts, supposed to produce painful diseases of the ovaries as well as menstrual disturbances. The *hormonic signs of retarded skeletal growth,* pointing so strongly to insufficiency of the anterior lobe of the hypophysis, should at least guard against early radical operations upon the female genitalia in these cases. An analysis of a considerable number of cases demonstrates conclusively that the pain, tenderness, and other distressing local signs, are possibly due to the deficiency of the pituitary secretion, rather than to local changes in any of the female generative organs. Further proof of this is shown in the courses of those cases, to be reported in this series in Section 3 on Pituitary Dysmenorrhea (page 385), in which operations have been performed on the strength of such indications. In all these cases there was absolutely no relief of the pain, tenderness, or other local signs present before operation. In fact, in nearly every instance, there was a marked increase of all these signs. This is additional proof of the theory that an insufficiency of the ovaries already exists in these cases, and that this insufficiency *is due to the withdrawal of the hormone from the anterior lobe of the pituitary, and that a primary disease of the ovaries is not* the cause for this abdominal pain. It would be just as rational to remove the thyroid in a case of cretinism or myxedema, as to remove the ovary in these cases in which the function of this organ is already reduced below the normal. If there is any indication in these cases for surgery, it would be to transplant more ovarian tissue, instead of removing that which is already unable to perform its function sufficiently to aid in the production of the normal menses. Primary blood dyscrasias, such as primary or secondary anemia, or blood-serum diseases which produce hemorrhagic conditions, must be taken into consideration in the differential diagnosis. The blood analysis in these cases demonstrates that there is not sufficient anemia to be a factor in the production of either the metrorrhagia or the amenorrhea. Abnormal coagulation time of the blood, as well as other diseases which show definite blood-serum reactions, can be excluded by blood analysis. Malaria, tuberculosis, cardiopathies, and other chronic infections and intoxications which produce marked secondary cessation of the menses, can usually be very easily ruled out by the history and signs of these diseases, either in the blood or in other organs of the body. The differentiation from those diseases which modify the skeletal growth, producing an infantile type of individual, such as true nanism, dwarfism, myxinfantilism, eunuchoidism, etc., has been discussed in Section 1, on Pituitary Amenorrhea, in which a pre-adolescent hypopituitarism of the anterior lobe was described. The same points in differential diagnosis relative to the pre-adolescent variety of this disease obtain with regard to the postadolescent type.

Complications, Sequelæ, and Associated Diseases.—This case, as well as most other hypopituitarisms in which the anterior lobe alone is involved, early in adult life, has had no complications or associated diseases. These primary insufficiencies of the anterior lobe of the hypophysis are very rarely complicated by other endocrinous gland dyscrasias, neither do they have the unusual susceptibility to other diseases which is present in those insufficiencies of this lobe occurring later in life. This difference, due to the age at which the inactivity occurs and the involvement of the anterior lobe alone, contrasts very markedly with that occurring in later life, or with additional involvement of the posterior lobe. It will be shown in the reports of these types of cases in the following pages, that in those cases occurring in late adult life or those in which there is bilobar involvement (both the anterior and the posterior lobes being affected) the most distressing chief complaints are those referable to such complexes as migrainous headache, dyspnea, syncopal attacks, severe gastro-intestinal disturbances (nausea and vomiting), incapacitating abdominal and lumbar pain, and extreme nervous manifestations. It is very rarely that any of these constitutional symptoms occur in pure anterior lobe insufficiencies. This can be accounted for by the function of the anterior lobe being almost entirely confined to the skeletal growth and the gonad function. The chief complaints referable to the insufficiency of the ovaries in the females of these cases occur only in those women who are anxious to bear children, who consequently frequently have secondary nervous disturbances due to their sterility, frigidity, or menstrual abnormalities. Not infrequently, however, late in life (after the age of thirty-five), even these patients with pure primary anterior lobe deficiencies begin to have peculiar nervous attacks, associated with an unusual type of headache. These are described as peculiar sensations, as if the patient were "losing her mind." There are unusual lapses of memory and extremely irritable periods of excitation, during which the patients feel that they are not absolutely responsible for their actions; and yet they are cognizant of every act and state present during this time. Peculiar disturbances of the eyes are present during these short attacks, for which they frequently consult oculists, who, on account of not finding any definite eye lesions, consider them neurotic individuals. These psychic states of emotionalism and excitation are sometimes diagnosed by competent neurologists as definite mental diseases. For instance, the writers have 2 patients who were considered positive cases of dementia precox, one being treated in one of the best private sanitaria in a neighboring state for a number of months for this disease. The largest majority probably consult the gynecologist for sterility and frigidity, and are frequently treated for local diseases of the genital system.

Clinical Varieties.—Case II reported herewith belongs to the pure anterior lobe insufficiencies occurring at or shortly after maturity. That the deficiency of the secretion of this lobe is not complete is indicated by the absence of continuous amenorrhea, as is present in Case I in a complete pre-adolescent hypopituitarism involving the anterior lobe of the hypophysis. It is interesting in comparing these two cases to draw attention to the difference in the menstrual history between the complete type occurring before adolescence, and the menstrual disturbance in the incomplete postadolescent type. In the complete pre-adolescent type, there is a continuous amenorrhea. In the partial insufficiency of the anterior lobe occurring later in life, there is more decided tendency to metrorrhagia. The withdrawal of this hormone, then, if its absence is decided or complete, has a tendency to stop the menstrual flow entirely. If this secretion is only partially withdrawn, clinical evidence has proved that there is decided tendency to profuse or prolonged scanty menstrual flow, interrupted by intervals of months of amenorrhea. This difference has led the authors to apply the clinical names of *pituitary amenorrhea* and *pituitary metrorrhagia* to these two clinical varieties. While these names are inaccurate on account of the marked variation occurring in different cases of exactly the same disease, it is hoped that these clinical terms will stimulate more investigation relative to the possible rôle of pituitary dyscrasia in the etiology of these menstrual disturbances. It must also be borne in mind that these pure anterior lobe involvements are frequently complicated later in the course of the disease by an additional affection, usually of hyposecretion of the posterior lobe. This, of course, changes the entire syndrome into a bilobar from a unilobar case in which the anterior lobe alone was affected. The onset of the posterior lobe inactivity is usually marked by the beginning of constitutional symptoms such as headache, substernal pressure associated with dyspnea, palpitation, and abdominal and lumbar symptoms. With the advent of these constitutional manifestations, there is usually a marked gain in weight, due to decreased metabolism. Localized deposition of fat is noted about the hips and the mammæ, producing the typical girdle, mons, and mammary adiposity so characteristic of bilobar hypopituitarism occurring in adult life. It must be noted, in addition, that this type may be later associated with pituitary neoplasm. The advent of intracranial pressure symptoms, particularly in these known cases of pituitary disease, such as intractable headaches, ocular perimetric deviations, and general intracranial pressure signs, as nausea, vomiting, etc., should lead to special and roentgenological reëxamination directed toward again determining the size of the sella turcica, the perimeter and fundus signs, etc.

Treatment.—PROPHYLACTIC.—The general principles of prophylactic treatment discussed under Case I will apply to this case of the same variety, occurring a little later in the development of the individual. Particularly in pituitary families, those individuals who have tendencies to retardation or arrest of skeletal development involving especially the short, flat, and peaked bones, should be carefully observed with regard to the hormonic signs of the anterior lobe of the pituitary gland. Probably one of the best means to corroborate an early suspected diagnosis of this disease would be the taking of regular measurements and *x*-ray examinations of the bones to determine the growth and development of the ossifying nuclei of the bones. It is true that this disease does not have the marked decided effect on the centers of ossification that is present in the cretin, whose osseous arrest can be excluded by the absence of other signs of early thyroid insufficiency. In any individual of such a family whose growth in height is not progressing to the normal, or whose short, flat, and peaked bones are not developing year by year, as could be determined by simple circumference measurements of the head, hands, and feet, prophylactic treatment should probably be considered. This treatment would consist in exhibiting anterior lobe extract or substance, as is done in the active treatment in those cases occurring later in life. After the menses have occurred in the postadolescent case, marked disturbances of ovarian function, as shown by the abnormal menstrual periods, associated with the skeletal abnormalities of anterior lobe hyposecretion, should indicate at once an attempt to intensively substitute the lacking secretion.

The ACTIVE TREATMENT in these pure anterior lobe insufficiencies of the hypophysis not due to pituitary tumor consists in the attempt to substitute the secretions of the anterior lobe of this gland. This is done by giving **anterior lobe of pituitary gland,** grains ii ss to xv (0.16 to 1 gram), three or four times a day, and **extract of anterior lobe of pituitary,** intramuscularly, minims xvi (1 c.c.) daily or at longer intervals, depending upon the amount required to relieve the menstrual disturbances in the female, or the impotence, loss of libido, and lack of development of the gonads in the male. In this case there was no other endocrinous glandular dyscrasia which required treatment previous to the direct treatment of the insufficiency of the anterior lobe of the hypophysis. In those cases associated with other ductless gland lesions, particularly insufficiency of the thyroid, the adrenals, etc., an attempt should be made to supply these deficient secretions to the individual before giving pituitary extract itself. In the majority of the pure anterior lobe insufficiencies, it will probably be necessary to give, besides the anterior lobe secretion, a form of secretion of the ovary or the testicle. The writers have obtained the most beneficial results with the following ovarian preparations: (*a*) **corpus luteum, grains v-x** (0.3 to 0.65 gram), by mouth, after meals; (*b*) **corpora lutea,** minims xvi (1 c.c.) intramuscularly, given daily or at not longer intervals than three days; (*c*) **ovarian substance,** extract from the stroma and corpus luteum of the ovary, minims xvi (1 c.c.) daily, or at not longer than three-day intervals; (*d*) **ovarian residue,** an extract from the stroma of the ovary, minims xvi to xxxi (1-2 c.c.) daily. The writers have obtained practically no beneficial results from giving testicular substance or its extract in pituitarisms or in eunuchoidisms in the male. They have derived some very good results, however, by **combining corpus luteum or ovarian substance administered hypodermatically, with the pituitary treatment** as given above, in these partial insufficiencies of the anterior lobe of the hypophysis in the female. It is always well, however, to try first the effects of the secretion of either the anterior lobe of the pituitary or the ovary (in the female) in order to determine absolutely just what single secretion, if any, will restore the individual to a normal state. This single glandular therapy, as will be repeated later in this series, is considered one of the most important therapeutic diagnostic tests in endocrine diseases. If it is carried out consistently in all cases, it unquestionably will be the means of clearing up to a large extent the diagnoses in these diseases. There are always at least two glands affected, one being the primary cause of the disease, and the other (gland) being disturbed in function secondarily by the effect on its activity of the hormonic secretion of the primarily diseased gland. For this reason, therapy, which consists of supplying one secretion alone in these cases, may help materially to demonstrate or exclude, if nothing more, the gland primarily involved in the production of the hormonic symptoms or signs which apparently come from two ductless glands. For instance, using this case as an illustration, if ovarian substance given in a way in which it would be most effective (as had been done) *does not produce any decided effect on the menstrual disturbances,* it would help to prove that insufficiency of the ovaries is not the primary cause. Then, if this treatment is followed by the administration of pituitary extract and substance of anterior lobe, either without or in combination with the ovarian secretions, with *beneficial results,* it would prove rather conclusively that the anterior lobe of the pituitary gland is the primary seat of secretory disease, and that the ovarian secretions are only secondarily modified by the withdrawal of its hormone—the secretion of the anterior lobe of the hypophysis.

Any other disease which might have a bearing on the functional secretion of either the anterior lobe of the pituitary or the ovary, of course, should be given the proper therapeutic consideration. It is well in all these cases to remember that *hereditary lues* is one of the most common diseases modifying the secretions of the ductless glands, and particularly of the pituitary. Even without any clinical or serological evidence as a basis for diagnosis of this disease, a **trial specific treatment** is not out of place, particularly in those cases which do not react to simple substitution treatment of the pituitary, in addition to the ovarian, extract and substance.

There are no special indications regarding other constitutional signs or symptoms. Certainly *nothing* can be accomplished by *diet, climate,* *hydro-, mechano-, or light therapy,* to relieve the *headaches,* the *retarded growth,* the *nervousness,* etc. *Roentgen* and *radium treatment* are absolutely *contra-indicated* on account of their effect of inhibiting, instead of increasing, the function or secretion of either the pituitary or the ovary. There is no means known to the writers for stimulating the secretion of the pituitary indirectly by inhibiting the secretion of other ductless glands, which might be accomplished by means of operation, radium, or roentgenological treatment. *Local treatment* directed toward the uterus or the ovaries has absolutely no effect. *Curettage, tampons, local electrical treatment,* cervical and replacement operations upon the uterus, etc., can have *no possible good result.* The **substitution** or the **polyglandular** treatment, as indicated above, must be continued in most cases more or less indefinitely. It is very rare that, in those cases in which a good result is obtained, the anterior lobe of the pituitary gland returns to normal activity, so that this glandular treatment can be entirely withdrawn. It frequently can be reduced to an injection once a month.

Prognosis.—The prognosis in this case is practically the same as in the pre-adolescent type of anterior lobe insufficiency, not due to pituitary tumor. As to life, prospects are always very favorable. As to relief of symptoms, the prognosis is always uncertain. With the treatment as known to-day, one is never in a position to say that satisfactory results can be obtained. It is hoped that an earlier recognition of these diseases will lead to a much more satisfactory prognosis with regard to the relief of symptoms and signs, particularly those bearing on the gonad function. As soon as the real cause of these metrorrhagias and amenorrheas existing in this type of cases is traced to the anterior lobe of the pituitary gland, and not considered local disease of the uterus or the ovaries, earlier and more persistent pituitary treatment will be given, which it is hoped will rapidly develop the treatment to the state where it will become still more effective. The prognosis must necessarily become unfavorable in those cases in which pituitary tumor later develops. Fortunately, comparatively few of this type of cases, according to the writers' experience, have undergone such unfavorable changes. It is very unlikely that even in the most favorable cases affected by simple substitution treatment, the function of the anterior lobe is able to be restored; so that prognosis as to the restoration of function in these cases, even in those reacting to treatment most advantageously, is unfavorable.

Pathology.—As has been said in the report of the previous case of pre-adolescent hypopituitarism involving the anterior lobe, the pathology of these early cases has not been absolutely established. The supposition is that there is a hypoplasia involving the anterior lobe. It is well known that there is a hyperplasia and adenomatous change in those cases of the opposite type, producing a hyperpituitarism, such as gigantism and acromegaly; but not a sufficient number of the very early simple primary anterior lobe insufficiencies have been controlled, either at autopsy or at operation, to give the absolute histological changes presented by these cases. The secondary changes due to the hormonic signs of withdrawal of the anterior lobe secretion are better known on account of the clinical and radiographic control which has been made in these cases. The skeletal undergrowth is particularly marked in these cases, which occur early in the life of the individual, at or immediately following adolescence. While this same undergrowth takes place in the thyroid, the adrenals, and the thymus, it does not produce the characteristic configuration of head, hands, and feet present in this disease. Besides the failure of development of the long bones and the characteristic pointing of the acral bones, there is undoubtedly a lack of development of the flat and short bones in this early hyposecretion of the anterior lobe of the hypophysis. The slenderness and delicacy of the peaked bones, producing, for instance, the small, narrow hand with tapering fingers, contrasts very markedly with the long overgrowth and tufted tuberosities seen in gigantism, and the wide, clubbed fingers present in acromegaly. Roentgenologically, the tapering terminal phalanx is usually free from tuberosities of any kind and has either persistent or well-marked traces of an epiphyseal line. In the male cases, the hips are usually broadened, and there is a tendency to genu valgum, with the other bodily accessories of the feminine type. Cushing states that there is one exception to the decreased size and the classical configuration of the hypopituitary head; that is, in those cases associated with pituitary tumor there is a maxillary prognathism instead of a mandibular prognathism as seen in hyperpituitarism. It is his impression that this is produced by forward displacement of the sphenoid bone, caused by the sella distention, with its consequent widening and projection of the superior malar prominence of the face.

The histological change in the gonads present in these cases is best illustrated in the male cases. Cushing describes three types of cases: (1) *Abundance of the interstitial cells of Leydig.* In this case the patient, only seven years old, had fully acquired the secondary sexual characteristics—enlargement of the genitalia, pubic and axillary hair, adolescent beard, masculine voice, etc. Nevertheless, the section of the testicle showed a pre-adolescent type of tubules, without spermatozoa. (2) *Paucity of the interstitial cells,* none of which could be identified as cells of Leydig. The patient, though of middle age, had never fully acquired the secondary characters of sex, possessing a feminine type of adiposity, hair distribution, etc. He nevertheless had been sexually active, and the testes showed a fully developed tubular epithelium, with spermatozoa. (3) *Development of the tubules, with a complete absence of interstitial cells.* In this individual there was an absence of secondary sex characters and an impotency. That similar changes to those found in the testicle take place in the ovary is probably true, but is very difficult to prove. This is due to the more decided lack of knowledge concerning the function and histological changes present in the ovary than what is known of the testicle. The process of ovulation and the formation of the graafian follicle is probably not related to the interstitial or stroma cells of the ovary. These cells, however, probably play a similar rôle to the interstitial cells of Leydig in the male testicle. Lemon has attempted to prove, at least, that there are similar cells in the stroma of the ovary to the interstitial cells of Leydig in the testicle of the male. Females upon whom operations have been performed, in which one ovary had been removed, or those cases of the female due to decided insufficiency of the anterior lobe of the pituitary, producing marked disfunction of the ovaries and absence of secondary sex characteristics, have been known to conceive and have children. The writers have one case under observation of a typical hypopituitarism involving the anterior lobe with skeletal undergrowth, marked disturbances of periods, and complete absence of secondary sex characteristics, who has given birth to five normal children. This probably proves that while there is a normal function of the graafian follicles of the ovary, there is, more than likely, a marked insufficiency of the stroma or the interstitial tissue of the ovary, which accounts for the absence of secondary sex characters. Cushing describes a patient with hypophyseal struma who has been castrated for the reason that her amenorrhea was thought to be the primary element of her malady. Her symptoms, as is constantly the case, were only aggravated by this procedure. The ovary in this case showed histologically no fully developed graafian follicles, although the woman was twenty-six years of age. *Large interstitial cells, however, were abundant,* and the presence of this tissue corresponded well with the adolescent characteristics, which were fully developed. The pathological change in the uterus in this variety occurring after maturity is not so characteristic as in the pre-adolescent type. The uterus is usually fairly well developed, and as far as can be made out by physical examination, is practically normal. Scrapings of uterine mucosa taken from curettements in these cases have never shown any definite changes which could be accountable for either hemorrhage or insufficiency of the gonads. The changes referable to other endocrinous glands and tissues of the body are practically negligible in anterior lobe cases occurring early in life. These cases differ materially from those occurring later in life, and also from the bilobar cases in which the posterior lobe is implicated. In the bilobar cases there is usually marked association of other endocrinous glands, particularly the thyroid and the adrenals, and pathological changes exist, due to other hormonic symptoms, in the tissues and organs of the body, produced by marked changes of metabolism and the deposition of fat. These are absent in this, as well as in the pre-adolescent type of anterior lobe hypopituitarism. The blood does not show any noteworthy changes, with the exception of an increase of both large and small lymphocytes. The blood-sugar in these cases is usually within the normal, and rises rapidly after the ingestion of the usual amount of glucose given for the carbohydrate tolerance tests. *This lack of carbohydrate tolerance helps to prove conclusively that the posterior lobe is normal in these cases.* Other evidence which would tend to substantiate this proof is the absence of other metabolic changes, deposition of fat, changes in blood-pressure, temperature, pulse, etc. The skin and the special sense organs are not affected, as they are in the bilobar type of pituitarism. In an occasional case of anterior lobe insufficiency occurring later in life, or in those early cases after this insufficiency has been present for fifteen or twenty years, eye symptoms do occur. These ocular changes are present in those cases, without pituitary tumor, and are not due to pressure on the chiasm or the motor oculi nerves.

SECTION 3

PITUITARY DYSMENORRHEA

(*Anterior Lobe Insufficiency, Postadolescent Aneoplastic Type*)

This section will include two illustrative cases of *dysmenorrhea,* due to a partial insufficiency of the anterior lobe of the hypophysis. That both of these cases had an inactivity of the anterior lobe is assumed from the specific osseous changes present in each, resulting from a withdrawal of the growth hormone of this lobe. Neither had definite evidence of any secretory anomaly of the posterior lobe. At the time of observation there was a history in Case III of a transient partial insufficiency of this lobe several years previous, but there were no definite signs of insufficiency of the posterior lobe of the hypophysis at the time of the first observation. In Case III the course and positive signs indicate a continuous partial insufficiency of the anterior lobe, dating from maturity. This was not sufficient to produce amenorrhea, metrorrhagia, or even to prevent conception. In Case IV the history revealed an early amenorrheic interval of seven months, following the initial menses. The subsequent course and physical signs would indicate that the anterior lobe secretion was normal until the age of twenty-three. During the following five years, to the time of observation, there was a progressive decrease in the function and hormonic secretion of the anterior lobe, without definite signs of posterior lobe inactivity. *Progressive dysmenorrhea* was added to the symptoms of both these cases in direct relation to the progressively decreased amount and duration of the menstrual flow.

Etiology.—The etiology in Case III is very uncertain. The past history shows the occurrence of measles, mumps, and "brain fever" (at the age of one and one-half years). Mumps has frequently been associated with endocrinous diseases, and its entrance into the history is always a suspected cause for pituitary disease. The "brain fever" might also have had a very decided effect in inhibiting this secretion, or possibly in producing a change in the pituitary gland, which had considerable to do with the disturbances of its secretion which occurred later in life.

Symptomatology.—HISTORY: CASE III.—Mrs. G. W. H., aged forty-five, General No. 2367, referred by Dr. John Young Brown, St. Louis, St. John's Hospital, June 17, 1918.

Present.—Chief Complaints: (1) Severe periodical *pain in the left hypochondriac region;* (2) dyspnea on exertion, related to a peculiar *heavy, sore sensation in the anterior chest;* (3) *intermittent headache,* not associated with ocular or gastric symptoms; (4) *abdominal disten-*

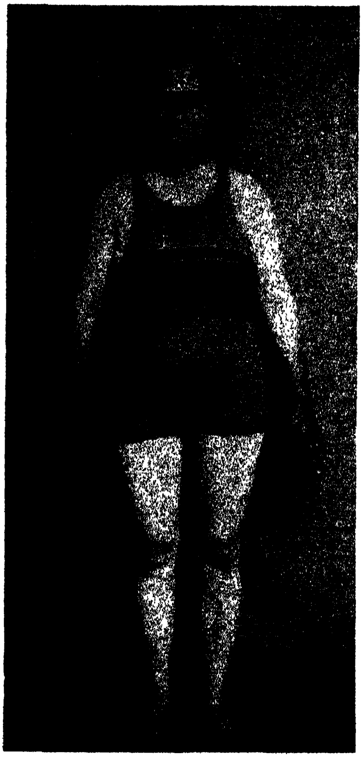
tion; constipation, associated with aching pain in the right lumbar region; (5) flexion *contracture of the second finger* of the left hand, so severe that vigorous massage is required to produce relaxation; (6) sensory disturbance of the left femur; (7) sudden pain in the left knee, so severe as to cause the patient to fall suddenly; (8) bladder irritation, associated with scanty micturition; (9) ravenous appetite for sweets; (10) *menstrual disturbances, scanty three-day periods. Menopause at the age of thirty-eight.*

Duration.—Nine years.

Course.—*Onset,* sudden, following a severe fall caused by sudden terrific pain in the left knee. Patient felt as if something had been dislodged in the left upper portion of the abdomen. Since then she has worn a stiff corset to support the left kidney, which she supposes has been displaced by this fall. Since that time the patient has suffered irregularly attacks of severe cramp-like, colicky pain, beginning in the left upper quadrant of the abdomen and radiating to the back and over the anterior portion of the abdomen. This pain has never radiated down the ureter or into the bladder. It has been so severe that medication was necessary for its relief, but hypodermics have never been required. No marked change in the amount or the character of the urine during or following these attacks, but during this entire time there has been a constant anuria. The headaches, the abdominal pain and distention, the constipation, the dyspnea, the sensory disturbances in the left leg, and the contracture of the second finger of the left hand occurred soon after the cessation of the periods at the age of thirty-eight. *Menstruation began at the age of sixteen.* The *duration* of each period was *three days,* and the amount of *flow was very slight, requiring only one pad* after the first day. The *periods were always regular,* but *very painful* during the first day or two of their duration. No history of metrorrhagia or amenorrhea, except during her pregnancies. The patient has conceived and borne five normal children. *At the age of thirty-eight,* while the patient was still nursing her last baby, the *menstrual periods,* which had recurred during lactation, *suddenly ceased.* Lactation also stopped at this time, and the other *marked constitutional symptoms—headache, dyspnea, abdominal distention,* etc.—began and have been present in various combinations during the seven years following this, up to the present time. These attacks of abdominal distention, constipation, headache, and dyspnea would recur at rather definite intervals of three or four weeks. Various kinds of treatment have failed to afford any relief of these symptoms. At the age of twenty-three, the patient weighed 89 pounds. Her weight remained practically stationary until the age of thirty-eight, when the periods stopped. *Since that time* (seven years) *the patient has gradually gained 30 pounds.* During these attacks of abdominal distention and constipation, associated with pain in the right and left hypochondriac regions, the patient has passed a considerable amount of mucus. These mucous defecations would usually terminate her attacks, and then she would be free from abdominal symptoms for a number of weeks, until another recurrence of the same complex.

Past.—Measles, mumps (in childhood), "brain fever" at the age of one and one-half years. No operations. Fall due to severe pain in the left knee, as described above.

Personal.—Menstrual history as described. *Five normal births,* normal children (*three nursed at breast*). No miscarriages. Appetite variable. Bowels constipated. Scanty amount of urine has been present for a considerable length of time. Drinks coffee moderately; no alcohol. Has special craving for sweets.



CASE III. Fig. 1.—Note Short Stature, Small Hands, Fragile Bones, and Slight Suggestion of Girdle and Upper Thigh Obesity.

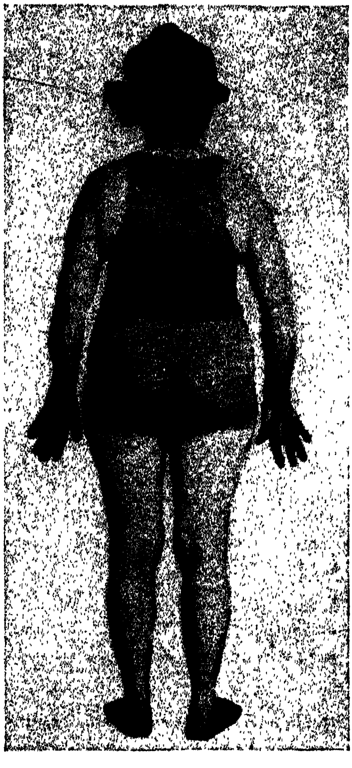


Fig. 2.—Posterior View. Note Axillary Padding, Suggestion of Girdle Obesity, and Small Hands and Feet.

Family.—Father died at the age of forty-five, cancer of the stomach. Mother died at forty-five, pneumonia. Five sisters living, one sister died of puerperal sepsis. No family history of ductless gland or hereditary diseases.

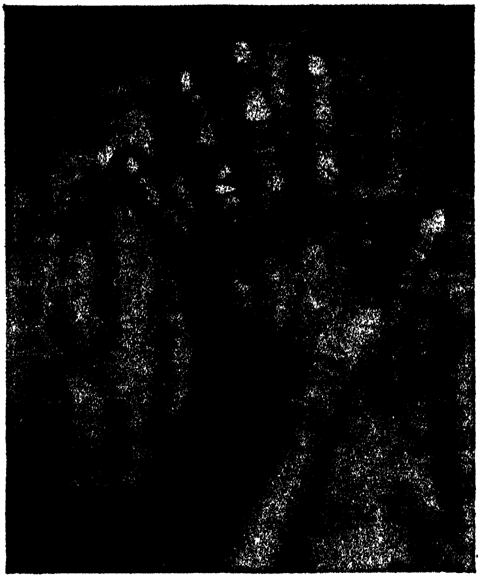
Examination.—*General.*—Extremely short, stocky type of woman, forty-five years of age. Head small, face very youthful, nose fairly straight, slight projection of the inferior maxilla. Extremely small, pudgy hands; patient unable to get gloves that will fit the wrists and not too long for the fingers. Fingers short, thick, do not taper. Feet unusually small (size of shoe, No. 1½). Lower teeth anterior to upper. Thyroid slightly enlarged. No abnormal distribution of hair. Chloasmic pigment about the forehead and the angles of the jaw. Slight girdle obesity—classical type, extending from the umbilicus to the junction of the middle and lower thirds of the thighs; slight fullness of the

CASE III. FIG. 3.—NOTE CHARACTER OF HANDS AND GIRDLE OBESITY.

mons. Breasts very small, virgin in type. No skin lesions; marked dilatation of venules about the hips and legs, varicose veins in both lower legs, slight scar on the right leg. Exposed surfaces of the body decidedly pigmented, due to the sun. Pulse, slow, regular, equal, symmetrical, low volume and tension. Temperament psychoneurotic. Blood-pressure: systolic 100, diastolic 60. Pulse (three days' observation), 68-80, temperature, 98°-98.4° F. (36.6°-36.8° C.). Measurements: Head to symphysis, 30 inches (76 cm.); from symphysis to soles of feet, 28 inches (71 cm.); height, 4 feet 10 inches (147 cm.); humerus,

.1½ inches (29 cm.); forearm, 8 inches (20 cm.); femur, 13 inches (33 cm.); leg, 13 inches (33 cm.); circumference of head, 21 inches (53 cm.); inferior maxilla, 16½ inches (42 cm.); neck, 11 inches (28 cm.); navel, 32 inches (81 cm.); lower thigh, 17¼ inches (44 cm.); upper thigh, 20 inches (51 cm.).

Regional (Positive Physical Signs).—*Head, small,* yet exceedingly *well proportioned,* hairline high. Considerable amount of *chloasma pigment about the forehead. Lanugo anterior to the ears, on the upper maxilla, and on the lips. Nose:* Typical *pituitary type,* bridge straight, no concavity at any point along its course, very slight rounding at the tip. *Mouth: Lower teeth project anterior to upper* (prognathism). All of the teeth were removed at the age of twenty-nine, on account of *early decay. Neck: Thyroid very slightly enlarged,* not vascular, slight increase in consistency, no thrill or bruit. Absence of fat cushions in the posterior and lateral cervical regions. No abnormal physical signs in the organs of the *chest* or *abdomen. Vaginal:* Perineum relaxed, vulva aplastic and infantile; uterus of normal size, anteflexed, very mobile, tubes and ovaries not palpable. *Extremities:* Miniature hands and feet (size of shoe, No. 1½); white crescents of the nails of the hands and feet absent, fingers and toes slightly enlarged at the tips, *not tapering.*

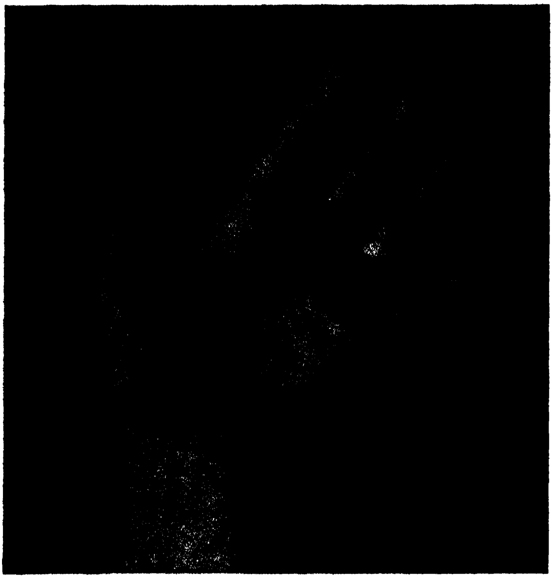


CASE III. FIG. 4.—NOTE SMALL HAND, BROAD PALM, AND SHORT FINGERS.

LABORATORY FINDINGS.—*Urine*—Single specimen, color straw, specific gravity 1.010, reaction alkaline. Albumin a trace, few leukocytes. Dextrose, erythrocytes, and casts negative.

Catheterized specimen, milky in color, reaction acid. Albumin, dextrose, leukocytes, erythrocytes and casts negative.

Feces.—Following blood-free diet, brown, formed. Mucus, pus, ova, parasites, and occult blood negative.



CASE III. FIG. 5.—PALMAR VIEW. NOTE BROAD HAND AND SHORT FINGERS, WITH TENDENCY TO TAPERING.

Blood:

Erythrocytes	6,050,000
Leukocytes	4,500
Hemoglobin	100 per cent.
Wassermann	negative

Differential Count:

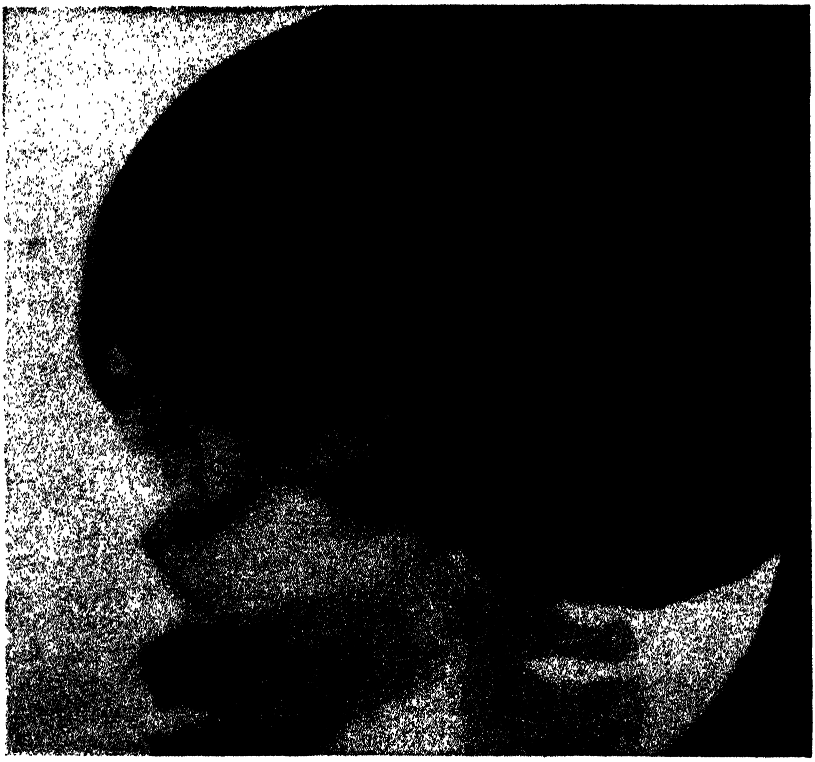
Neutrophilic leukocytes	32	per	cent.
Large lymphocytes	38	“	“
Small lymphocytes	23	“	“
Neutrophilic myelocytes	1	“	“
Eosinophilic myelocytes	3	“	“
Transitionals	2	“	“
Mononuclears	1	“	“

Blood-sugar:

(*a*) (Following 14-hour fast)	0.094	per	cent.
(*b*) (Two hours after ingestion of 93.2 grams ($3\frac{1}{3}$ ounces) dextrose)	0.144	“	“

SPECIAL EXAMINATIONS.—*Fluoroscopic.*—*Head, neck, chest, heart, vessels, mediastinum, diaphragm, stomach,* free from abnormal signs.

Trochoscopic.—Rectal pouch very small, spastic. Spasticity involving particularly the iliac and pelvic colons, to a lesser extent the descending colon. Transverse colon normal in width, very freely mobile. Splenic flexure can be separated. Cecum very high, slightly immobile, three fingerbreadths above iliac crest. Appendix visualized, small, curved up under cecum. No ileocecal valve incompetency



CASE III. FIG. 6.—SELLA TURCICA SMALL.

Roentgenogram of Skull: Sella turcica small.. Other markings normal.

Diagnosis: *Hypopituitarism, Incomplete Anterior Lobe Insufficiency* (with slight posterior lobar inactivity), *Late Adolescent Variety, Aneoplastic Type.*—The diagnosis of an incomplete anterior lobe insufficiency of the hypophysis in this case is made upon the association of the very decided arrest of growth of the skeleton, with evidence of a partial insufficiency of the gonads, as demonstrated by the late maturity (at the age of sixteen), the very scanty, imperfect periods, and the extremely early menopause. Following the climacteric at the age of thirty-eight, there probably was a slight hyposecretion of the posterior lobe, as evidenced by the tendency to slight girdle obesity and the gain of weight of 30 pounds within the seven years following this time. That there was only very slight, if any, insufficiency of the posterior lobe of the pituitary gland present at the time of observation is proved by the *absence of decided girdle obesity* and *of an increased sugar tolerance.* It will be noted from the carbohydrate tolerance test that there was a rise in the blood-sugar of from 0.094 to 0.144 within two hours after giving 93.2 grams (3⅓ ounces) of dextrose (Janney-Isaacson method). This absence of sugar tolerance is as marked in this case as in the previous two (Cases I and II), in which there was more definite evidence of independent anterior lobe insufficiency, as shown by the completely negative evidence of posterior lobe hormonic signs.

On account of the patient's conceptions and pregnancies, the diagnosis in this case might be questioned. Cushing has shown, however, that when the secretion from the *anterior lobe is not markedly decreased,* there are retained in the female some functions of the ovaries. This function pertains more especially to the corpus luteum and its secretion than to the possible internal secretion derived from the stroma of the interstitial tissue of the ovary. Cushing has shown in these cases that, while there is a paucity in the development of the graafian follicles concerned in ovulation and reproduction, these follicles are nearly always present in the ovaries removed from these cases; and furthermore, that ovulation, conception, and pregnancy have frequently occurred in the cases in which the secondary sexual characteristics and libido have been entirely absent. He used this as a proof that the graafian follicle and corpus luteum development most probably had no relation to the sexuality and the secondary sexual characters of the individual. These traits characterizing this development probably have their source in the stroma or in the interstitial substance of the ovary. The scanty three-day period and dysmenorrhea which were persistently present throughout the duration of the course of this case, taken with the very early climacteric, would certainly indicate at least a partial insufficiency of the ovaries. The history, in the presence of such a decided classical skeletal configuration, probably suffices to group this case among the late partial insufficiencies of the anterior lobe of the hypophysis. The fact that there was no other etiological factor to account either for the infantile growth or for the character of the menses, the late adolescence, and the early menopause, makes this explanation more convincing. The negative roentgenological signs for enlargement of the sella turcica, and the absence of intracranial pressure symptoms, exclude the possibility of pituitary neoplasm.

The marked constitutional symptoms, such as headache, dyspnea, abdominal distention, abdominal pain, and constipation, present in this case, contrast decidedly with Cases I and II of anterior lobe insufficiency, described in the preceding sections. These constitutional symptoms are rarely, if ever, present in the cases occurring in pre-adolescent or early adolescent life, but do occur occasionally in the pure anterior lobe insufficiencies of late adolescent life. Their presence, however, should always lead one to suspect a possible involvement of the posterior lobe. They have been so constantly related to inactivity of the posterior lobe secretion, that the writers have begun to have considerable confidence in ascribing them almost entirely to posterior lobe secretory defects. That there was an insufficiency of the posterior lobe, at least for a time, immediately following the cessation of the menses in this case, is probably true. The history of gain in weight, associated with slight girdle obesity, concomitant with the onset of headache, dyspnea, abdominal and other disturbances, allows one to be fairly certain that the posterior lobe became insufficient for a few years during the course of the patient's disease. That there was no insufficiency of this lobe up to the time of the menopause, however, is also conclusively proven by the negative history of late posterior lobe hormonic signs. It is more than likely that in this case (Case III) a considerable amount of the abdominal pain was produced by the spasticity of the colon, associated with a mucous colitis. Roentgenological examination demonstrated a very decided spasticity of the descending, iliac and pelvic colon. The history was a positive one for mucous colitis, consisting of severe abdominal pains and cramps, followed by the evacuation of a large amount of mucus, with complete relief of the preceding abdominal symptoms. The sudden attack of pain in the left knee, producing a fall, was probably due to a floating cartilage, although this was not demonstrated definitely by roentgenograms of the knee. It is difficult to explain the cause of the contractures of the fingers. It is more than likely that the sensory disturbances were a part of the hypopituitarism of the anterior lobe. There was no diagnostic evidence of other endocrine gland involvement, with the possible exception of the thyroid, which was, in all probability, very slightly insufficient. This insufficiency is to be suspected on account of its frequent association with late adult hyposecretions of the pituitary, rather than on account of any definite signs of thyroid insufficiency noted in the individual.

Complications, Sequelæ and Associated Diseases.—In this case, these were absolutely insignificant. The floating cartilage in the left leg had no relation to the hypopituitarism. The spastic colitis and the mucous colitis possibly had some relation to the pituitarism. Spasticity of the colon, however, is more frequently related to hypersecretions of the posterior lobe than to independent anterior lobe insufficiencies or to bilobar insufficiencies of the hypophysis. It will be noted that this individual was absolutely free from other infectious diseases, as is usually the case with the pure anterior lobe abnormality. These cases contrast very strikingly with the bilobar insufficiencies occurring later in life, which types are very susceptible to other infections, such as rhinitis, bronchitis, tonsillitis, rheumatism, etc.

Clinical Varieties.—These late partial insufficiencies of the anterior lobe do not have any decided presenting symptom or complex which characterizes them as independent clinical varieties of hypopituitarism. They do not have enough hormone insufficiency to produce either marked amenorrhea or metrorrhagia, as has been shown in the very early or the adolescent cases. They may have just enough withdrawal of the secretion of the anterior lobe to produce more or less *dysmenorrhea.* Nevertheless, there has not been sufficient proof for one to say definitely that their painful menses are entirely due to anterior lobe deficiency. Experience with a number of exactly this type of case possibly warrants the suggestion that it is particularly this clinical variety, occurring at this age, of less marked inactivity of the anterior lobe, which is accountable for the dysmenorrheas. Therapeutic proof, in the form of constant relief of the dysmenorrhea present in this variety of case, by substituting extract and substance from the anterior lobe of the pituitary gland, has so far been missing. This cause should be borne in mind, however, as an etiological factor of dysmenorrhea, particularly when it is present in the classical, arrested skeleton configuration, which is easily recognized because of the fact that it is produced by more or less complete withdrawal of secretion or reduction in function of the anterior lobe of the hypophysis. If this theory has any basis for its conception, it would finally add, to those which have already been mentioned, another clinical group of inactivities of the anterior lobe—namely, (1) *pituitary amenorrhea,* complete inactivity of the anterior lobe of the hypophysis occurring at the pre-adolescent age; (2) *pituitary metrorrhagia,* incomplete insufficiency of the anterior lobe occurring during or shortly after adolescence; and (3) *pituitary dysmenorrhea,* partial inactivity of the anterior lobe, more frequently occurring late in adolescence. While it is conceded that the above clinical groups are to a certain extent unsubstantiated and their foundation not grounded upon either good scientific investigation or sufficient clinical evidence, the writers have suggested them as a diagnostic means of *attempting to measure the amount of inactivity of this gland existing in the different clinical groups of cases.* They have considerable confidence in the clinical division of pituitary amenorrhea; but whether the pituitary metrorrhagias and the pituitary dysmenorrheas really depend upon the amount of insufficiency of the secretion or the reduction in the function of the gland, remains an open question. It is one, however, that can probably be more definitely established rather by very careful clinical and therapeutic observation than by other scientific investigation.

Treatment.—Treatment in this case would consist of the treatment outlined in the previous sections, discussed in a general way under the treatment of anterior lobe hypopituitarism. It would be important in this case first to attempt to overcome the partial suspected insufficiency of the thyroid, in order to determine the effect of this treatment upon the constitutional symptoms, particularly the abdominal pain, etc., for which the patient presented herself for diagnosis. After the **thyroid treatment** had been given to tolerance without complete relief of symptoms, **pituitary treatment**, consisting of anterior lobe preparations, and, if this is unsuccessful, the addition of posterior lobe substance, should be exhibited. Symptomatic treatment, directed toward the spasticity of the colon and the floating cartilage of the knee-joint, is also indicated. Treatment directed toward the independent symptoms, such as the abdominal pain, etc., has been absolutely without effect. This is the history which is obtained in all these cases regarding such medication.

Prognosis.—The prognosis in this case with regard to life is favorable; with regard to relief of symptoms, uncertain. The effect of treatment would be an additional important prognostic guide. For example, if all the distressing symptoms were completely relieved by pituitary therapy, with the addition of thyroid treatment, not only would the prognosis be favorable, but the diagnosis would be absolutely confirmed.

Pathology.—As this patient is still living, the absolute pathological changes are unobtainable. With regard to the pituitary gland, it consists possibly of an aplasia of the anterior lobe of the gland, without very decided histological changes in the infundibulum or the posterior lobe. The deficiency of this lobe was not due to a new growth of the pituitary, as there was both roentgenological and clinical evidence excluding such a neoplasm. The change in the thyroid was probably that of a colloid adenoma. The pathological changes in the bones, the slight adiposity, etc., were characteristic of the hormonic effects of withdrawal or reduction in secretion of the anterior, and possibly of the posterior, lobe of the hypophysis, previously described.

CASE IV

Etiology.—The presence of a diphtheria during the time of maturity in the following case (IV) probably has some very definite bearing upon the consequent hypopituitarism. It has long been known that severe diseases, either infections or intoxications, occurring at the age of adolescence, are very frequently followed by marked abnormalities of the menses. The common conception of the relation of these adolescent diseases to menstruation has been that they involve directly either the ovaries or the mucosa of the uterus in order to produce their subsequent abnormal effects. It is possible that a better understanding of the pituitary control over the gonads will probably establish the fact that it is the effect of these diseases upon the pituitary gland, particularly of the anterior lobe, which produces secondary abnormal functions and changes in the gonads, with their consequent disturbed menstrual history. That this case was not due to new growth in the pituitary gland, at least up to the time of observation, is proved by the small sella turcica and the absence of intracranial pressure symptoms. The sociological aspect of these diseases of the anterior lobe is a very important one. Their sterility, impotence, and loss of sexuality are factors which render these individuals to a large extent unfit for marriage and procreation. The effect of this gonad disturbance upon the nervous system is also one which is quite decided. This pertains probably more to the female than to the male. One is frequently struck by the nervous irritability and instability into which the formerly well-balanced individual changes after marked menstrual disturbances have been present for a comparatively short duration. For this reason, if for no other, more decided effort should be made to unravel these secretory anomalies of the anterior lobe of the pituitary, after the accomplishment of which more potent treatment will undoubtedly be developed to restore the activity of a normal sexual state.

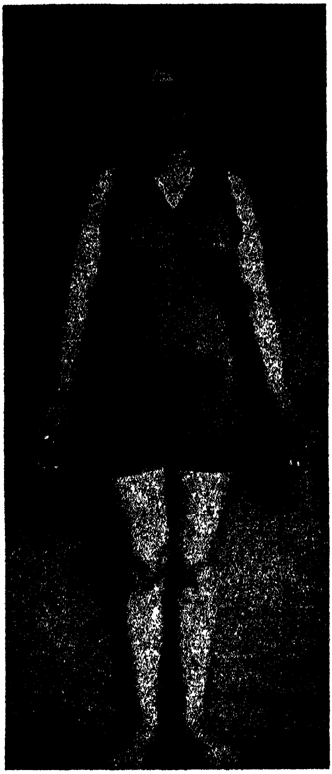
Symptomatology.—HISTORY: CASE IV.—Mrs. M. S., aged twenty-seven, General No. 2401, St. John's Hospital, St. Louis, June 24, 1918, referred by Dr. F. E. Skinner, DeSoto, Mo.

Present.—Chief Complaints: (1) *Pain in the left inguinal region,* increased by exercise or standing, radiating down to the hip; (2) *dull headache, vertex in location,* occurring during the premenstrual week; (3) *constipation,* associated with dizziness; (4) *pain in the lumbar region;* (5) *swelling of the hands and feet* a few days *previous to the menses;* (6) *palpitation;* (7) *gaseous distention of the abdomen;* (8) *marked decrease in the duration and amount of the menstrual flow.* During the past five years there has been a change from a normal five-day menses to a very slight, scanty flow, of two days' duration, accompanied by increasing dysmenorrhea.

Duration.—Of pain in the inguinal region, three years; of menstrual disturbances, five years.

Course.—(*a*) *Onset* of pain in the inguinal region, sudden. While walking along the street the patient was seized suddenly with a severe, sharp, lancinating pain in the left iliac region, radiating down the left leg. This was so severe that the patient was forced to sit down. After a short time, the pain was relieved, and she was able to continue.

(*b*) *Progress.*—This pain has recurred at regular intervals during the past three years. Three weeks ago she was seized with a severe attack of this pain, which has been more or less constant up to the present time. The pain is of a gradual, steady, aching variety, radiating down the left leg. No radiation occurs to the bladder or vulva. The menstrual disturbances occurred two years previous to the onset of this pain. The first menses occurred at the age of fourteen, at which time the patient was very ill with diphtheria. After the initial menses, *no period occurred for seven months.* The periods then returned and were apparently normal until the age of twenty-three. Previous to this age (with the exception of the first seven months of amenorrhea), the periods were of five to seven days' duration, with abundant flow, requiring four or more menstrual pads daily. The regularity was exact and they were free from pain. Following the age of twenty-three, the periods gradually decreased in amount, until *the age of twenty-five, the average duration of flow being only three days, very scanty,* requiring only one, or, at the most, two pads during the first day or two of the menses. *From the age of twenty-five to the present time* (two years), *they have been changed to a one-day period,* during which there is only *a very scanty flow,* requiring, at the most, one menstrual pad. Up to the age of twenty-three, the periods were absolutely painless. *Since that time they have become more and* *more painful,* until, *during the past year, there has been marked dysmenorrhea.* No flow or bleeding occurred at irregular intervals or between the periods. The interval between the periods has been regular and of the twenty-eight-day duration. During the past three years there has been a very slight, gradual gain of weight, but during the past five months she has lost 25 pounds. The patient has been *married nine years, but has never conceived,* and has had a *marked tendency to frigidity. The headache and the swelling of the hands and feet have usually occurred during the few days or the week previous to the menses.*



CASE IV. FIG. 1.—NOTE ABSENCE OF MARKED OSSEOUS UNDERDEVELOPMENT, IN NATURE OF FRAGILE BONES AND SMALL HANDS, AND VERY SLIGHT FULLNESS ABOUT UPPER THIGHS, WITHOUT CLASSICAL GIRDLE OBESITY.

Past.—Measles, diphtheria. No operations, no injuries.

Personal.—Appetite good. Bowels constipated. Burning on urination, more marked previous to menses. Drinks coffee moderately, no alcohol.

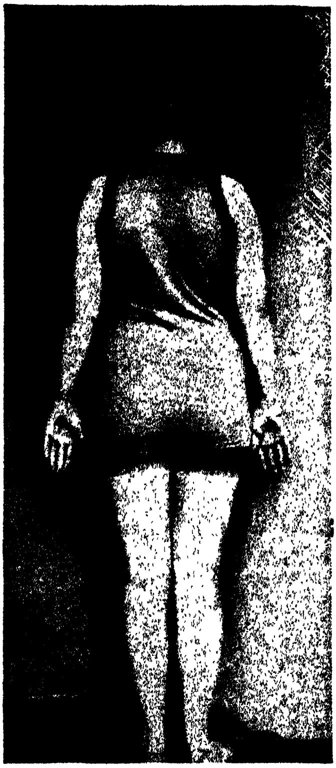
Family.—Father living, fairly well. Mother living, has female trouble. Mother of medium size, 5 feet 6 inches in height, weighs 145 pounds; she has swelling of the hands, feet, and abdomen. Two brothers living, one has kidney trouble. Husband living, well. No family history of tuberculosis, cancer, liver trouble, or other hereditary diseases.

EXAMINATION.—*Physical.*—Exceedingly well proportioned and nourished individual, 5 feet 9 inches in height, weight 150 pounds. *Very slight chloasma on the temporal regions and around the mouth, occasional small spot on the neck,* body free from this pigment. *No abnormal distribution of hair. No localized obesity,* very slight fullness about the upper portions of the thighs, but no typical girdle adiposity. *Proportions almost perfect. Hands show slight tendency to clubbing at the tips of the fingers, absence of white crescents at the bases of the nails,* fingers rather long, wrists not narrow. No separation of the upper incisors. No edema, cyanosis, or dyspnea. No abnormal gait, station, or position. Pulse, slow, regular, equal, symmetrical, low volume and tension, no special type. Temperament, psychoneurotic. Pulse rate, 80-88; temperature, 98°-98.8° F. (36.6°-37.1° C.).

CASE IV. FIG. 2.—NOTE DIFFERENT CHARACTER OF HAND AS COMPARED WITH PRE-ADOLESCENT ANTERIOR LOBE HYPOACTIVITY. IN THIS CASE, INCREASED LENGTH OF FINGERS AS COMPARED WITH PALM WILL BE NOTED.

Regional (Positive Physical Signs).—*Head:* Well proportioned, with classical features; lanugal hair anterior to the ears. *Mouth:* Slight irregularity of the upper incisors, teeth almost perfect, some tiny filling of the posterior molars. *Neck:* Slight fullness over the thyroid, no distinct enlargement. *Chest:* Lungs and pleuræ negative. *Heart,* normal; blood-pressure, systolic 130, diastolic 80. *Abdomen:* Absolutely no girdle obesity; tenderness over the femoral ring on the left side, no definite impulse on coughing, in the lying position; in the standing position, pain limited to the femoral opening on the left side, and impulse on coughing elicited; marked tenderness in the left iliac region above Poupart's ligament; other abdominal organs normal. *Vaginal:* Uterus normal in size and position, freely mobile; very slight tenderness in the left fornix, but no evidence of infiltration or enlargement of the tubes or ovaries. *Extremities* and *reflexes,* normal.

LABORATORY FINDINGS.—*Urine.*—(*a*) Specimen clear, specific gravity 1.010, faintly acid reaction. Albumin, dextrose, erythrocytes, and casts negative. Few leukocytes and epithelial cells. (*b*) Catheterized specimen, color amber, acid reaction. Albumin, dextrose, erythrocytes, and casts negative. Few leukocytes. (*c*) Twenty-four-hour specimen, 1,300 c.c., color straw, specific gravity 1.012, acid reaction. Albumin, dextrose, leukocytes, erythrocytes, and casts negative, epithelial cells present.



CASE IV. FIG. 3.—POSTERIOR VIEW. NOTE ABSENCE OF GIRDLE OBESITY.

Feces.—Following blood-free diet, brown, soft. Mucus, pus, ova, and parasites negative. Occult blood positive.

Stomach Content.—Ewald test meal, sour odor, color pink, chymification poor. Free hydrochloric and lactic acid negative (?) Mucus, bacilli, and blood negative. (Water used to remove test-meal.)

Blood:

Erythrocytes	5,300,000
Leukocytes	7,600
Hemoglobin	104 per cent.
Wassermann	negative
Differential count:	
Neutrophilic leukocytes	43 per cent.
Large lymphocytes	50 " "
Small lymphocytes	5 " "
Transitionals	2 " "

Sugar Tolerance Test (Blood-sugar):

(*a*) (Following 14-hour fast)	0.070
(*b*) (Two hours later, following ingestion of 120 grams (4¼ ounces) dextrose by mouth)	0.104

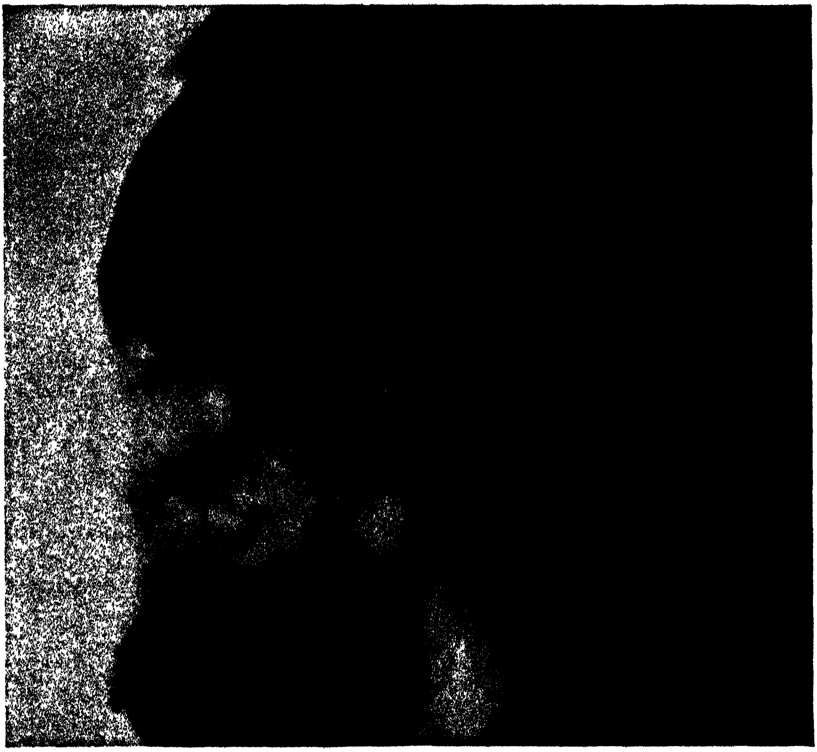
Special Examinations.—*Fluoroscopic.—Head, neck, lungs, heart, diaphragm, stomach,* normal.

Trochoscopic.—Colon, normal.

Roentgenogram of Head.—Sella turcica small, other markings normal.

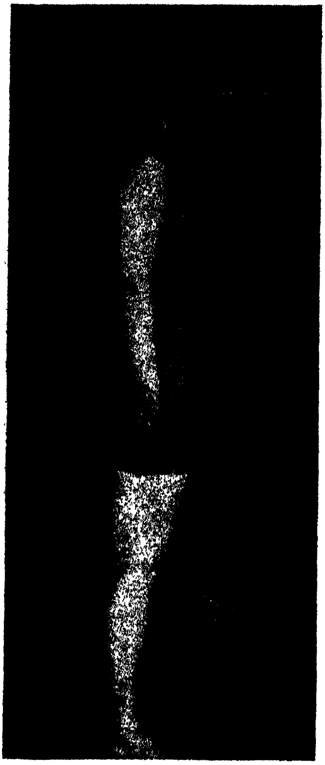
Diagnosis: *Partial Anterior Lobe Insufficiency, Postadolescent Variety, Aneoplastic Type.*—This case has been included in the reports of this series as an illustration of the partial, incomplete or aberrant types of anterior lobe insufficiency occurring in the adult life. It will be noted that nearly all other cases which have been described have been advanced, classical cases. These cases were accepted as the most profitable ones for description for two reasons: (1) In these advanced, outspoken diseases, the diagnosis, although based only upon clinical signs, is much more positive. (2) It is these cases which lend themselves best as examples for the demonstration of the gross and easily recognized hormonic signs. These complete, advanced cases, however, are rather the exception, while it is the milder, incomplete or aberrant form of these cases which occurs most frequently. Yet, if the decided hormonic signs are once known, the same physical or clinical signs presented in lesser degree will be more easily picked out by the observing clinician.

The only evidence of anterior lobe insufficiency found in this case is that referable to the function of the gonads. The marked change of the periods from a normal five-day period to a very scanty one-day type, the sterility and the frigidity, the absence of local and general diseases which might cause such changes, point very strongly toward secretory inactivity of the anterior lobe of the hypophysis as the cause of the atypical menses. One of the most constant menstrual disturbances recurring in hyposecretion of the anterior lobe of the hypophysis is a very decided early *cessation of the periods occurring during the first year of maturity.* The seven-month amenorrhea which followed the initial period in this case, leads one to suspect very strongly that there was a partial insufficiency of the anterior lobe at maturity. This was overcome entirely for a number of years, only to recur later at the age of twenty-three and to progress decidedly until the age of twenty-five, when dysmenorrhea was then added, increasing in severity to the time of observation. The physical signs indicating anterior lobe insufficiency in this case are extremely meager. There was only slight abnormal pigmentation, consisting of chloasma impregnation of the skin around the temporal regions, the mouth, and the angles of the jaw, extending down the lateral aspects of the neck. There was also some clubbing of the fingers, with absence of white crescents at the bases of the nails. Besides this, there was a history of *enlargement of the fingers and feet previous to periods*, which is very characteristic of anterior lobe insufficiency. The slow pulse and the subnormal temperature, in the absence of other causes, indicate hyposecretory disease, but not especially pituitary insufficiency. The absence of obesity, with the presence of decreased sugar tolerance, demonstrates that this is a pure unilobar disease in which the posterior lobe has not been implicated. The pain in the right side of the abdomen radiating down the leg was probably



CASE IV. FIG. 4.—NOTE SMALL SELLA TURCICA.

due to a femoral hernia, and is considered an entirely independent lesion having no relation to the progressive dysmenorrhea or insufficiency of the anterior lobe of the hypophysis. The roentgenological examination of the sella turcica, with the history and negative perimeter signs of the eye, muscle paralysis, etc., demonstrates the absence of an enlargement of the pituitary gland. There was no focal or local change in the gland itself which would confirm the diagnosis of pituitarism.



CASE IV. FIG. 5.—NOTE HANDS, MORE CHARACTERISTIC OF GONAD DEFICIENCY, AND VERY SLIGHT FULLNESS ABOUT THIGHS AND ABDOMEN, WITHOUT TYPICAL GIRDLE OBESITY.

In such a case, it will probably be necessary to have therapeutic confirmation of the diagnosis to make it convincing. This would consist of a return toward the normal of the menses, as to both duration and amount, and relief of the dysmenorrhea, produced by substituting extract from the anterior lobe of the hypophysis. If, in addition to the effect upon the periods, there were relief of the headaches, the abdominal distention and pain, and the enlargement of the hands and feet during the premenstrual week, this would prove conclusively that all these symptoms are due not only to hypopituitarism, but to definite inactivity of the anterior lobe of the pituitary gland.

The DIFFERENTIAL DIAGNOSIS in this case would consist of excluding other local diseases, particularly of the ovaries and the pelvis, and other general diseases which might have a tendency to reduce or stop the menses entirely. Provided the diagnosis of the left femoral hernia can be accepted, there was no other cause for the pain in the left lower abdomen. The vaginal examination did not reveal any definite adnexal or intrapelvic disease as a local cause for the changes in the menses. Examination of the other organs in the body, the blood, the urine, etc., did not reveal evidence of other disease which might explain the entire symptom-complex. The general nutrition of the body, the good proportions, the condition of the musculature, the color, and all the general clinical manifestations help to exclude general infections, intoxications, etc., as a possible cause for either the abdominal pains or the marked decrease in the menses. Eunuchoidism could be excluded by the absence of the osseous disproportions of this disease, as shown by the development of the long bones of the extremities and those of the hands.

Complications and Sequelæ.—This case demonstrates, as has been mentioned previously, the usual freedom from complications, sequelæ, and associated diseases which is characteristic of pure anterior lobe insufficiency. The femoral hernia in this case is taken as a merely incidental defect, having no relation to the primary pituitarism.

Clinical Varieties.—This case would be classified under the clinical variety of *pituitary dysmenorrhea,* for the reason that it has neither the complete amenorrhea nor the metrorrhagic disturbances of those more marked inactivities of this lobe occurring earlier in life. It goes to prove the general conception of the theory that patients with incomplete or aberrant anterior lobe insufficiency probably complain more of painful and scanty menses than of definite evidence of complete cessation or of prolongation of their menstrual flow.

Treatment, Prognosis and Pathology.—The treatment, prognosis and pathology in this case do not differ in detail from those amenorrheic or metrorrhagic cases which have been defined in previous discussions.

SECTION 4

PITUITARY TUMOR

A. Posterior Lobe Insufficiency, Pre-adolescent Neoplastic Type

Etiology.—The importance of trauma, which has been frequently referred to by authors (Cushing and Aschner), is well illustrated in the following case. Especially is this true of trauma at the base of the skull, which, however, was not present in this instance. This would also help to prove some relationship, as has frequently been quoted by older writers, between trauma and diabetes insipidus and glycosuria.

Symptomatology.—HISTORY: CASE V.—Master J. N., aged fourteen, schoolboy, General No. 748, St. John's Hospital.

Present.—*Chief Complaints:* (1) *Vomiting;* (2) *pains in the head,* radiating to all portions of the head; (3) *disturbances of vision;* (4) *disturbance of gait;* (5) *difficulty of urination;* (6) *inability to lie on the back on account of pains in the head;* (7) *fainting spells, epileptiform attacks.*

Duration.—Probably four years.

Course.—(*a*) *Onset,* gradual. Four years ago the child *fell about thirty feet, striking on the lower portion of the back,* and was picked up unconscious. After recovery, he played around with the other children. Recovery from this fall seemed to be complete.

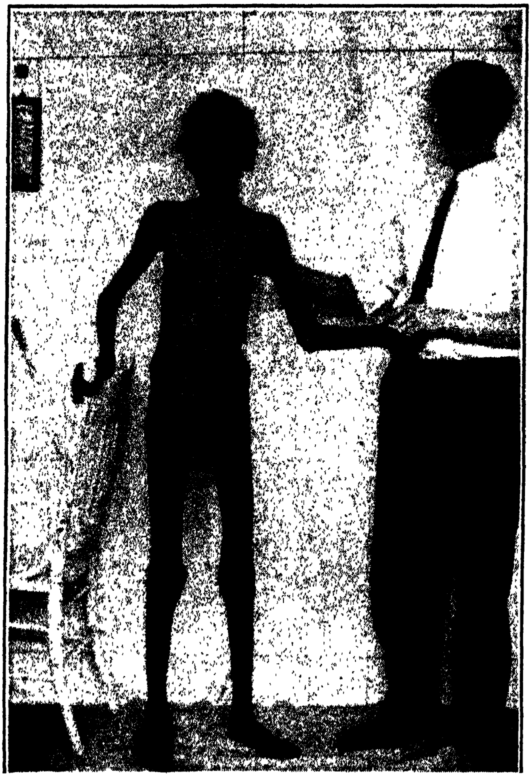
(*b*) *Progress.*—Following this, *the patient for some time passed an unusual amount of urine.* One year ago, while in school, he noticed white spots before his eyes, and had to be escorted home. Following this, double vision occurred, pains in the head appeared, and became gradually worse. The patient was up and around, but complained next of difficulty in urination, walking became more difficult, vision was more affected, and finally, thirteen weeks ago, he was confined to bed. Vision, pains in the head and neck, and vomiting, without nausea, became gradually worse. The patient's diet has never been abundant, on account of the poverty of the parents. The patient was in Mullanphy Hospital, St. Louis, seven weeks ago, where a diagnosis of brain tumor was made. He remained in the hospital twenty-four hours, was returned to his home, and his condition became gradually worse up to the time of his entrance to the present service.

Past.—Measles. Denies other childhood diseases.

Family.—Father living, aged thirty-eight, very anemic. Mother living, aged thirty-five, well. Seven brothers and sisters, well. No family history of tuberculosis, syphilis, etc.

Note.—History indefinite on account of its source, through a friend of the patient. Patient too somnolent to answer questions.

Examination.—*General.*—Schoolboy, aged fourteen, height about 5 feet 5 inches, very emaciated, so that the joints appear very much enlarged. Muscles and soft tissues between the joints are considerably atrophied, bony markings throughout the entire body very pronounced.



CASE V. Fig. 1.—Note Extreme Height, Unusual Length of Long Bones, Long Distance from Symphysis to Soles of Feet, Absence of Obesity, and Well-developed Genitalia.

Patient not able to stand alone, but able, by holding on, to bear weight on legs. Proportion: Long bones overdeveloped, hands and feet practically normal in size for age; genitalia of normal size. No abnormal distribution of hair about the body or extremities. No abnormal pigmentations or skin lesions. Hair on the head, eyebrows, and eyelids, very thick and well developed; no hair on face except a very slight growth at the angles of the mouth. Color: Nails very anemic, skin colorless, not impregnated with any other color. Skin harsh, very slight desquamation over the arms, none on malar processes. Pulse, slightly increased in rate, quick, sharp, increased in volume and tension, no special type, rhythm good. Respiration slow and regular. No cyanosis, dyspnea, or edemas. Patient is dull, apathetic, not stuporous, reacts to stimuli, answers questions imperfectly, complains of pain in the back of the head. Marked divergence of the right eye. Retraction of the abdomen marked, iliac regions and symphysis prominent, ribs show through skin rather distinctly. Temperature, 97.6°-99.2° F. (36.4°-37.3° C.); pulse, 86-120; respiration, 16-28.

Regional.—Head: Marked difference in percussion note on the two sides of the head, much higher on the right than on the left. Auscultatory percussion of the head shows marked difference in the two sides. Considerable tenderness on pressure over right occipital region, posterior pressure produces pain in this region. Considerable pressure on the right side, bilateral compression produces pain. No cracked-pot sound, no tenderness over sinuses, muscle insertions, or occipital nerves, with moderate pressure. *Eyes:* Sight almost entirely gone, can distinguish light from darkness, not able to distinguish (count) fingers, or recognize ordinary objects such as lead pencil. Cannot distinguish colors. Marked divergence of the right eye; turned slightly upward and outward. Pupils dilated, right pupil larger than the left. Right eye will not turn farther than median line to the left. Pupils do not react to light or accommodation. Scleræ clear, no marked pigmentation in the lids, lid movement normal. *Nose:* Septum deviated slightly to the left, some obstruction on that side. Hypertrophy of inferior turbinate. Mucous

CASE V. FIG. 2.—NOTE LENGTH OF LONG BONES AND LONG, THIN TAPERING FINGERS, PRODUCING EUNUCHOID HAND.

membranes normal. *Ears:* Bone conduction good, heard in the right ear without obstruction of the canal, in the left ear with obstruction. Rinne's test negative. *Face:* No special type; nose, lips, or chin not blunt or rounded. Seventh nerve intact. *Mouth:* Lips, mucous membranes, well colored. Teeth in good condition, slight pyorrhea. Pharynx injected. Tongue deviates markedly to the left. *Neck:* Some voluntary fixation of the neck, which is not absolute. Patient able to move the neck backward and forward, but the muscles are fixed. Deviation of vertebræ to left in the third and fourth cervical region, and considerable tenderness over the left side of the upper cervical vertebræ, from the skull down to about the fourth or fifth one. Prominent swelling and bulging, due to scoliosis of the vertebræ in this direction. Marked prominence of the vertebræ, down as low as the lower cervical, anteriorly, to the left, reaching from the bodies of those vertebræ down to the clavicle. Prominence of the body of the vertebra in the pharynx, anteriorly, posterior pharyngeal wall, anterior projection. The body of the vertebra is felt through the mouth, and there seems to be more projection toward the left. Thyroid not enlarged, very few palpable glands, no marked venous or arterial pulsation. *Chest:* Shows signs of general emaciation, bony markings prominent, clavicles and scapulæ made out very distinctly, no adipose tissue, skin seems to be in contact with the bones. Posteriorly, no abnormal signs on percussion or auscultation. Anteriorly, percussion resonant throughout. Normal vesicular breathing, no increased transmission of spoken or whispered voice, no râles or rubs. *Heart:* Apex beat, in the fifth interspace, well within nipple line. Heart vertical. Considerable impulse in the third and fourth interspaces, impulse markedly palpable over entire precordium. No diastolic shock or thrill. Sounds moderately rapid, pure, and regular. *Abdomen:* Long, narrow, acute intercostal angle. No scars or pigmentations, no visible peristalsis. Slight epigastric pulsation. Abdomen very much retracted, tympanitic throughout, including deep in the flanks. *Liver:* Dullness four fingerbreadths above costal arch to costal arch, edge not palpable. *Kidneys:* Right kidney not palpable. *Spleen:* Not enlarged to palpation or percussion. *Colon:* Squashing sounds in cecal region, cecum not palpable. Sigmoid not palpable. *Genitalia:* Testes very small, genitalia otherwise normal. *Rectal:* External and internal hemorrhoidal veins not enlarged, prostate not palpable, no ballooning of the rectum. *Extremities:* Long bones well developed, considerable emaciation, skin dry, harsh. No varicosities or edemas. Eunuch hand. *Reflexes:* Babinski, elicitation on the left produces fanning of the toes, without distinct dorsal flexion of the great toe, no response on the right. Chaddock, Gordon, Oppenheim, negative. Achilles not elicited. Forearm, biceps, triceps, very sluggish, radioperiosteal not elicited. Chvostek present, jaw-jerk sluggish.

LABORATORY FINDINGS.—*Urine Analysis.*—(*a*) Single specimen, yellow in color, acid in reaction, dextrose negative, moderate trace albumin, casts, leukocytes, and erythrocytes negative.

(*b*) Twenty-four-hour specimen, 650 c.c., cloudy, alkaline, specific gravity 1.010, dextrose negative, albumin, casts, leukocytes, and erythrocytes negative.

(*c*) Twenty-four-hour specimen, 990 c.c., alkaline, specific gravity 1.012, dextrose, albumin, casts, leukocytes, and erythrocytes negative.

(*d*) Twenty-four-hour specimen, 450 c.c., cloudy, alkaline, specific gravity 1.020, dextrose, albumin, casts, leukocytes, and erythrocytes negative.

(*e*) Twenty-four-hour specimen, 660 c.c., cloudy, alkaline, specific gravity 1.010, dextrose, albumin, casts, leukocytes, and erythrocytes negative.

(*f*) Twenty-four-hour specimen, 1,040 c.c., pale, cloudy, alkaline, dextrose negative, faint trace albumin, occasional cast, erythrocytes negative.

Blood Analysis:

Erythrocytes	4,500,000
Leukocytes	9,000
Hemoglobin	85 per cent.
Stained smear	normal differential count
Wassermann	negative

Sugar Tolerance Test:

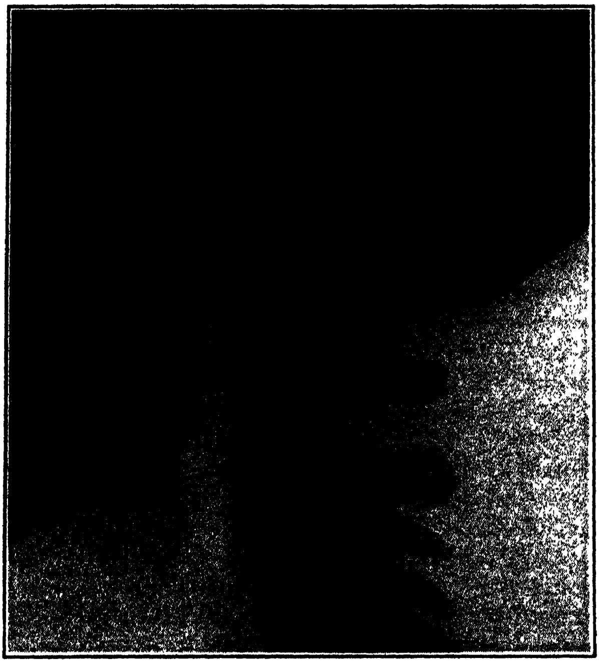
(*a*) Negative Glycosuria.
(*b*) Following 100 grams (3½ ounces) glucose, no glycosuria in twenty-four-hour specimen urine.

SPECIAL EXAMINATIONS.—*Roentgenogram of Head.—Marked enlargement of the sella turcica.* Thinning of the skull areas over the frontal region. Posterior suture line visible.

Ophthalmic.—Fundus: *Complete optic atrophy,* complete loss of vision (perimeter chart impossible).

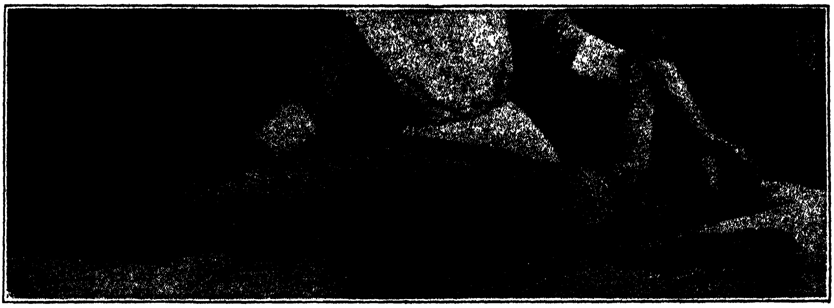
COURSE AFTER LEAVING HOSPITAL.—The patient died three weeks after leaving the hospital, from increased intracranial symptoms, cachexia, and coma (autopsy refused).

Diagnosis: *Hypopituitarism, Posterior Lobe Insufficiency without Anterior Lobe Involvement, Pre-adolescent Variety, Neoplastic Type.*—The diagnosis of this case is based upon: (1) the objective evidence of pituitary tumor—an enlarged sella turcica, blindness, optic atrophy, general and regional symptoms of intracranial pressure, etc. The roentgenogram proves rather definitely that the sella turcica was enlarged from a pituitary tumor and not from a neighborhood tumor arising from other structures. (2) The history in the case of an early diabetes insipidus, followed in a short time by disturbances of vision and finally total blindness, showed that the posterior lobe of the pituitary gland was the original source of the tumor. This polyuria changing to a normal urinary output or anuria, helps to prove that there was an overactivity of this lobe which finally changed into a decreased or inactive function of this portion of the pituitary body. (3) The presence of overdevelopment of the long bones and the well-developed genital organs tend to prove that the *secretion from the anterior lobe* was not materially decreased. In fact, the eunuchoid development (unusual development of the long bones, etc.) and fairly large genitalia would speak for an overactivity of the anterior lobe, combined with a deficiency of the internal secretions of the gonads. *Aschner and Goetsch both maintain that the posterior lobe of the pituitary inhibits the internal secretion of the gonads.* There is evidence of an early hypersecretion of the posterior lobe of this gland in this case at the age of ten years, after the gonads had been practically developed. If inhibition of these glands (testicles) occurred at that time, this would explain their size and yet allow sufficient cause for the length of the long bones. The signs of *anterior* lobe sufficiency are shown by the absence of the skeletal retardation and aplasia of the genitalia. If the epiphyseal junctions were open and their ossifying centers still receptive to activation, the exciting hormone for these centers from the *anterior lobe* would naturally be expected to produce an increase in the length of the long bones. This fact will clearly explain the differences in the size and dimensions of the long bones present in the insufficiency of the posterior lobe of the pituitary, depending upon the time, *i. e.*, during the activity of the epiphyseal ossification. It will not, however, explain the absence of obesity which should be present in the insufficiency of the posterior lobe due to reduction in the metabolism, particularly the catabolism. The cause for this absence of



CASE V. FIG. 3.—NOTE MARKED ENLARGEMENT OF SELLA TURCICA. POSTERIOR SUTURE LINE VISIBLE. (Defect in plate.)

adiposity in this case probably lies in the fact that during the early course in this case, there was hypersecretion of the posterior lobe of the pituitary, as was evidenced by the polyuria associated with intracranial symptoms. It is known that hypersecretions of this lobe induce emaciation, rapid absorption of the adipose tissue, etc., producing the typical non-obese stature. When later, in the course of this case, this hyperactivity changed to hypo-activity of this lobe, which ordinarily produces the classical girdle obesity, the intracranial symptoms were so extreme that they caused nausea, anorexia, vomiting, a limited intake of food, and a marked rapidity of the course of the disease, thus preventing the adiposity. This, however, might be reason for questioning the classification of the above case among the hyposecretions. The increased sugar tolerance and the subnormal temperature indicate inactivity. This is taken as a case of pure posterior lobe disease, that is, one in which there is no evidence of anterior lobe disturbance.



CASE V. FIG. 4.—"SHOWING PATIENT'S EMACIATION AND INFANTILISM." (From Cushing's "The Pituitary Body and Its Disorders." Ed. 1910.) Classified by Cushing as a case of dyspituitarism. Note absence of obesity and similarity in stature to Case V, reported herewith.

Cushing and others have classified similar cases under this group without giving any definite explanation for the absence of adiposity. Other positive controlled cases (operative or autopsy) with their corresponding histological evidence, would also lead one to such a classification. Yet the clinical picture of this type (particularly the physical signs) is so different from the better known dystrophia adiposogenitalia, that the diagnosis and consequently the classification of this disease are made difficult.

Complications and Sequelæ.—There were no special complications or sequelæ in this case. The individual died a short time after leaving the hospital from intracranial pressure symptoms, cachexia, marasmus, convulsions, and coma, a death very similar to that occurring in animals caused by a prolonged injection of pituitary substance, added to pressure of intracranial tumor growth. Cushing reports, in a similar case, enlargement of the thyroid and skin pigmentation, probably due to insufficiency of the adrenals.

Clinical Varieties and Types.—The classification of this case is based upon the grouping of these diseases arranged in the introduction to this article, in which the pituitary diseases were divided into lobar groups. In order to properly classify these cases there must be a *more clear-cut understanding of the hormonic signs and symptoms* produced by each lobe of this gland. Those due to the posterior lobe must be carefully distinguished from those due to the anterior lobe. Our discriminating knowledge must go *even farther, and differentiate the constitutional signs and symptoms* of those pituitary secretions or *hormone effects due to overactivity* from those due to *underactivity of a single lobe.* The differentiation of the hormonic signs of the *anterior lobe* from those of the *posterior lobe* will be given in the next section, in which a postadolescent posterior lobe insufficiency will be described. Analysis of the signs and symptoms due entirely and purely to the *anterior lobe* have been given in detail in Section 1. This place has been selected to reassemble and analyze the *hormonic signs of the posterior lobe.* A hormonic sign of this lobe will again be defined as the chemical change produced in metabolism (sugar tolerance and adiposity), the physiological alteration of functions (blood-pressure, temperature, and pulse), and physical or histological changes in other organs (osseous, dermal, nervous, muscle, or other endocrine glands or excretions), caused by a disordered function or secretion of the posterior lobe of this gland. In assembling the hormonic signs of the *posterior lobe* of the pituitary, those due to *overactivity* will be contrasted in separate columns with those due to *inactivity,* as given in Table 3.

The hormonic signs due to increased and decreased activity of the posterior lobe are given in detail. It will only be necessary to refer to the fact that they are exactly opposite, a statement that cannot be proved absolutely on account of the considerable difference of opinion regarding the functional effects of this lobe, as related to specific influence upon other processes and structures of the body. It will be observed that the writer is of the opinion that this lobe of the hypophysis has practically no relation to the growth or function of the osseous and genital systems. On the contrary, its function is limited directly to the regulation of the metabolism, and indirectly to effects upon other organs and tissues which deal with metabolic procedure.

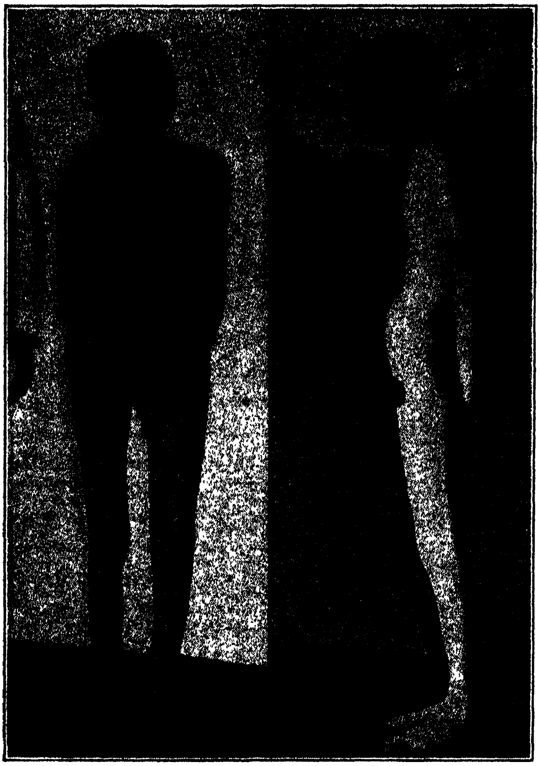
The influence of the secretion of the posterior lobe upon metabolism, estimated from personal observations based upon the determination of basal metabolism and carbohydrate tolerance, was found more definite in its relationship than those changes of metabolism associated with the simple anterior lobe dyscrasias. The following is a summary report of the basal metabolism and carbohydrate tolerance determinations made upon cases of pituitary disorder in which the posterior lobe was involved independently, or was associated with an anterior lobe syndrome. Many of the cases having anterior lobe disorder had a secondary gonad disturbance, but none was of the pluriglandular syndrome having hormonic signs of the thyroïd, adrenals, or other ductless glands. The *basal* *metabolism* determinations were made in 18 cases in which the posterior lobe was involved. Of these, 14 cases were hypoactivities, and 4, hyperactivities. In the hypoactivities, this metabolism was decreased in 5 cases, normal in 5 cases, and increased in 4 cases. Of the 4 cases showing an increased metabolism, against the rule for hypoactivities of this lobe, it occurred in 2 after treatment, and in 1 associated with a polyuria. This practically left only 1 case which had an increase in metabolism, not conforming to the supposition that decreased secretion of this lobe is constantly associated with decreased metabolism. Of the 4 hyperpituitarisms, the metabolism was increased in 2, and normal in 2, all fitting perfectly into the clinical diagnosis.

TABLE 3.

HORMONIC SIGNS OF THE **POSTERIOR** LOBE OF THE HYPOPHYSIS

	HYPOPITUITARISM	**HYPERPITUITARISM**
I. **Metabolism**	I.	I.
(*a*) Basal Metabolism	(*a*) Decreased	(*a*) Increased
(*b*) Carbohydrate Tolerance	(*b*) Increased	(*b*) Decreased
(*c*) Glycosuria and Hyperglycemia	(*c*) Absent	(*c*) Present
II. **Adiposity**	II. Marked girdle, mons and mammary	II. Absent, usually emaciation
III. **Polyuria**	III. Present (Pars intermedia?)	III. Absent (or present with glycosuria)
IV. **Involuntary Muscle Contraction**	IV.	IV.
(*a*) Intestinal	(*a*) Absent; frequent intestinal atony	(*a*) Present; frequent intestinal spasticity
(*b*) Uterine	(*b*) Absent	(*b*) Present
V. **Endocrine Secretion**	V.	V.
(*a*) Thyroid	(*a*) Hypoactivity (hibernation)	(*a*) Hyperactivity
(*b*) Adrenals	(*b*) Insufficiency?	(*b*) Hyperactivity?
(*c*) Gonads	(*c*) Hypoactivity (with anterior lobe disorder)	(*c*) Hyperactivity (with anterior lobe disorder)
(*d*) Pancreas	(*d*) Normal (increased sugar tolerance)	(*d*) Hypoactivity (decreased sugar tolerance)
VI. **Nervous State**	VI. Apathy: Somnolence frequent	VI. Psychic instability
VII. **Temperature**	VII. Subnormal	VII. Normal
VIII. **Pulse**	VIII. Slow	VIII. Rapid

In 61 cases diagnosed as posterior lobe disorders, the *carbohydrate tolerance* was determined. Of these 61, 3 were grouped with the hyperactive variety, in 2 of which the sugar tolerance was increased, and in 1, decreased. In 58 cases a diagnosis was made of hypoactivity of this lobe, which showed in 53, an increased, and in 5, a decreased sugar tolerance. A recent contribution by Rohdenburg, Bernhard and Krehbiel, upon the study of the sugar mobilization, based upon 228 cases (cancer, tuberculosis, thrombo-angiitis, cirrhosis of the liver, myocarditis, etc.), discredits to a considerable extent the value of the carbohydrate tolerance test in metabolic disturbances. They conclude that in other conditions, as widely different as diabetes, tuberculosis, epithelioma, and pregnancy, a blood-sugar curve is found, similar to that in metabolic disturbances, that many of these conditions are accompanied by hyperglycemia, and that concentration of the blood-sugar is not the sole factor concerned in the development of glycosuria.



CASE V. FIG. 5—"PITUITARY DYSTROPHY IN A MAN OF FORTY. HEIGHT, 5 ft. 2 in. NOTE ADOLESCENT FIGURE, ABSENCE OF OBESITY, AND ABSENCE OF HAIR ON FACE AND PUBIC REGION."

(From Hewlett, Arch. Int. Med.) Note also well-developed genitalia and general similarity of stature to Case V, reported herewith.

The classical obesity, interpreted as a "hormonic" sign of posterior lobe hypopituitarism, consists of girdle- and mons-adiposity, to which, in some cases, is added mammary adiposity. There is yet considerable controversy concerning the cause of this obesity. Its character and location have suggested secondary gonad insufficiency as its origin, because this frequently accompanies the bilobar cases with anterior lobe insufficiency. An argument against this cause of the obesity is that it is absent in the pure anterior lobe insufficiency in which there is complete aplasia and absence of function of the gonads. The writer has observed cases of this kind, in females, aged thirty-six and thirty-eight years, in which there was complete amenorrhea and infantilism of the genitalia during the entire life, without the development of this typical adiposity. The emaciation which is present in hypersecretion of this lobe is easily accounted for on the basis of increased metabolism. The rapid loss of weight and emaciation frequently accompanying hypophyseal polyuria, however, is more difficult to explain, particularly if this polyuria is attributed to decreased secretion of the posterior lobe. If both these functions (polyuria and adiposity) are attributed to hyposecretion of the posterior lobe, then we should obtain adiposity much more frequently with the diabetes insipidus syndrome, which, clinical experience demonstrates, is more constantly associated with emaciation. Biedl has reported some exceptional cases, however, in which this peculiar combination of adiposity and polyuria occurred. It is not uncommon to have a history of early transient polyuria, followed later by adiposity, which might be due to a change of activity of this lobe. Bab's theory that the polyuria is due to *hyposecretion* of the pars intermedia, not including the pars nervosa, seems to approach nearer to an explanation of the clinical combinations, as well as to account for the therapeutic relief which many of these patients obtained from hypophyseal treatment. The argument that this polyuria is really due to hypersecretion, on account of the fact that it is associated with so many other symptoms of posterior lobe hypersecretion, such as increased metabolism, decreased sugar tolerance, hypophyseal glycosuria, emaciation, and bladder and intestinal tenesmus, has not been entirely disproved.

The control of the contraction of the unstriped muscles, particularly those of the intestine and uterus, as well as of the bladder and the vascular and bronchial systems, is one of the most striking and easily demonstrable effects of the secretion of the posterior lobe. The writer has used the constriction effect of this substance upon the intestinal muscle ("intestinal reaction") to define the tolerable dose of pituitary extracts in the treatment of posterior lobe insufficiency. Extracts of the posterior lobe are given in varying dosages, to the amount producing definite intestinal cramps, followed by evacuation. This reaction occurs within ten or fifteen minutes after giving this substance hypodermatically. The dosage at which this reaction occurs is taken as the normal physiologic dose, and increase above this amount for therapy is deemed inadvisable. If a larger dose is given, that which is described as a "general reaction" occurs. This consists of tremor, tachycardia, and emotionalism. The effect of extracts of this lobe upon the nervous system is strikingly demonstrated by giving so intolerable and untoward a dose. Mental symptoms from so large an injection, consisting of emotional attacks, crying, laughing, shouting, and, in some, definite brainstorm, simulating temporary insanity and obsessions, have been produced. The "intestinal reaction" was tested by the writer for its diagnostic value, to determine whether the amount of extract producing these intestinal symptoms might not indicate to some degree the sufficiency of the posterior lobe. It was thought originally that cases having a deficient secretion from this lobe would require a much larger injection to produce the "intestinal reaction" than those with a normal or increased secretion. While it was found that the cases of hypopituitarism usually required a larger dose for the production of this reaction, this did not occur constantly, or in a sufficiently larger percentage to justify a positive interpretation.

The effect of posterior lobe secretions upon the other endocrine glands is not absolutely defined. The fact that a hypothyroid state is frequently associated with hypopituitarism, especially if it occurs in late adult life, which produces a combination that is believed necessary for the production of pituitary hibernation, has led to the conclusion that hypoactivity of the thyroid more frequently accompanies decreased function of this lobe. It has also been noted that peculiar hyperthyroid states have been frequently associated clinically with hyperpituitarism of the posterior lobe. This relationship may possibly be accountable for the increased basal metabolism and decreased sugar tolerance present in these cases, and it might help to explain the discrepancies existing in basal metabolism determinations made in pituitary disorders.

The adrenals are supposedly insufficient in the hypopituitary, and hyperactive in hyperpituitary disorders of this lobe. The peculiar pigmentation (chloasma) so frequently found about the hair-line, angles of the mouth, eyes, lateral aspects of the neck and nipples, has been taken by the writers as a sign probably associated with the anterior lobe disorders, and not due to the adrenals. This is thought to be true on account of its frequent presence in positive hypophyseal cases which are entirely free from other signs of adrenal disease, such as disturbed blood-pressure, marked asthenia, diarrhea, and other symptoms.

It has been stated by some authors (Fischer, Falta and others) that the hypersecretion of the posterior lobe has a marked inhibitory effect upon the gonads, as well as a stimulating effect upon the mammary gland. Personal observation in the writer's cases has led to the conclusion that Bell is probably correct in stating that this relationship does not exist. In those cases of pituitary disease in which the function of the gonads was disturbed, this was attributed to the hormone from the anterior, and not from the posterior lobe. Four cases with pure posterior lobe pituitarism showed marked changes in metabolism and carbohydrate tolerance, adiposity, etc., in which no abnormal changes, either in function or development, of the genitals could be demonstrated or were on record.

Pemberton and Sweet assign to the secretion of the posterior lobe an inhibitory influence upon the pancreatic secretion. It is known that there is a marked increase in the sugar tolerance in hypopituitarism, and yet there is uncertainty as to whether hypoactivity of the pancreatic secretion is present in this condition. The nervous makeup of the individual is markedly affected in changes of activity of this lobe. In decreased secretion, apathy and somnolence are frequent. In hypersecretion, marked periodic psychic instability, of various degrees and moods, is very common. The temperature, pulse, and blood-pressure correspond well to the activity of any other endocrine gland, being subnormal in decreased secretion, and normal (or at times there is a slight pyrexia, hypertension, and tachycardia) in increased secretion of this lobe.

As this and the following case (VI) are taken as illustrations of the clinical type of *pituitary tumor,* it is thought at this place desirable to add the detailed manifestations of localized intracranial pressure referable to neoplasm of the pituitary gland, whether it involves the posterior, the anterior, or both lobes of the hypophysis. These manifestations can be divided into those producing (1) general constitutional disturbances, and (2) focal signs or symptoms of pressure upon neighborhood structures near the *pituitary gland* or the *sella turcica.* The general signs of intracranial pressure do not differ from those present in other intracranial growths. The most important are (*a*) headache, (*b*) photophobia, (*c*) nausea and vomiting. The headache is not one that is characteristic of this lesion alone. It is usually severe in type and located frequently at the base of the skull anteriorly and posteriorly. Many patients, however, complain of an intense headache of undefinable location. It varies greatly in duration and intensity and frequently is absent for a considerable length of time without known reason. Photophobia is a common symptom. There is complaint of sensitiveness or irritation located in the eyeball or at the back of the eye, accompanying distress when the patient is exposed to the light. All of these symptoms are occasionally relieved by the patient's being in the dark. The vomiting is typical of that accompanying intracranial pressure, consisting of the projectile variety, associated with only very slight and frequently no nausea, gastric or abdominal signs—such as pain and tenderness.

The most important *focal disturbances* of the pituitary neoplasm are: (1) deformity of the sella turcica, (2) ocular signs, (3) pressure upon the brain, (4) nasopharyngeal signs. The deformity of the sella turcica occurs only in those cases of this variety due to actual tumor of the pituitary. It must be remembered that *there is a large percentage of these diseases of the pituitary gland without tumor,* and hence *with no deformity of the sella.* In those cases of *pre-adolescent hypopituitarism* in which there is a very small head, an *unusually small sella turcica* is present. This point is emphasized for the reason that there is very little mention made of it in the literature. It has been found so commonly associated with the personal observations of the writers that as much importance has been placed on the small sella in this particular variety of the decreased secretions of the pituitary as is ordinarily attributed to the enlarged sella turcica in those types of pituitary disease due to neoplasm. The deformities of the sella turcica vary from the very slightest defect in the transverse diameter or increase of its depth to a complete destruction of all of its wall, with the resulting roentgenographic picture of the entire absence of the posterior clinoid process, with decompression through the anterior wall of the sella into the nasopharynx. The deformities of this bony cavity are best demonstrated by stereoscopic roentgenogram, which shows the sella as if one were looking into it from above and behind. An occasional transverse view of the skull in which the *sella has not been properly focused* will be quite deceptive, in neglecting to show the exact size of this small cavity. It is necessary to compare the size of the sella in two directions with the entire size of the skull, in order to arrive at the exact information with regard to its comparative size. Its normal size is given by Cushing as anterior-posteriorly, 5/8 inch (1.5 cm.), and vertically, 3/8 inch (1 cm.). Keith gives the measurements of a normal sella turcica as, anteroposterior diameter, 3/8-1/2 inch (0.93-1.2 cm.), and vertical diameter, 3/8 inch (0.93 cm.). The *ocular symptoms* produced by tumefaction of the hypophysis are due to pressure upon the chiasm and the intracranial nerves (third, fourth, and sixth), interfering with the eyeball movement. The pressure of the chiasm produces blindness in certain portions of the retina with its consequent perimeter deviation. As has also been previously stated, this blindness does not consist of an absolute exact bitemporal hemianopsia, as is frequently stated in the text. It varies according to the size, or the degree to which the chiasm is affected, and also depends upon the intensity of the pressure in those rapidly growing tumors which decompress themselves anteriorly through the sphenoid into the nasopharynx. This pressure will constantly vary, and consequently a decided change in the hemianopsia is present throughout the course of the case, as was illustrated in the case herewith reported. Choked disk, which is ultimately followed by complete optic atrophy, is frequently a terminal finding in those cases not modified by decompression or early death. Paralysis of the third, fourth, and sixth nerves will produce consequent deviation in the axis of the eye affected, with the resulting diplopia, strabismus, etc., depending upon the nerves or the combination involved.

Pressure upon the uncinate gyrus produces the attacks of epilepsy or epileptiform attacks so frequently associated with pituitary disease. These attacks frequently have as a part of their aura or post-convulsive state *subjective disturbances of smell or taste.* The writers have at the present time several cases of petit mal and 8 cases of grand mal in typical hypopituitary individuals, who have constant gustatory disturbances during the aura or following each attack. There are also under observation other hypopituitary individuals whose chief complaint is that of almost constant odor, as for example, of ether, associated with a bitter taste. The nose of one of these patients was treated by a rhinologist, her amenorrhea by a gynecologist, and her nervousness and alopecia by a neurologist, for a considerable length of time, without benefit.

Pressure upon the *peduncles* of the *cerebellum* is frequently responsible for disturbances in gait and ataxia. This was present in the case herewith reported. Pressure posteriorly, attributed to pineal gland and other tumors, is responsible for an *anterior hydrocephalus*. Many interesting cases are found in the literature, in which the lateral ventricles, through the obstruction located in the region of the pineal gland, have produced pituitary pictures associated with dilated ventricle extreme enough to shell out the cerebellum almost completely. The *nasopharyngeal sign* is one in which there is a discharge of a considerable amount of mucus into the nose. When these cases are associated with more or less intense headache, they are frequently treated for a time for supposed sinus disease. The flow of cerebrospinal fluid into the nose, or *cerebrospinal rhinorrhea,* has resulted in some cases in which the pituitary neoplasm decompressed itself through the sphenoid sinus.

Treatment.—The treatment in this case is undoubtedly early **surgical interference.** It is entirely different from cases which have no focal manifestations of enlargement of the pituitary gland or intracranial pressure symptoms (Case 1). **Organotherapy, x-ray, radium,** and other forms of therapy certainly should be reserved for postoperative instead of preoperative treatment. If the relationship between diabetes insipidus, or polyuria with glycosuria, and the hypophysis were sufficiently appreciated, these cases would undoubtedly be diagnosed earlier. The present high mortality from the operative procedures, attempted many times after choked disks, complete blindness, and other marked intracranial pressure symptoms predominate, would necessarily be reduced if this treatment were instituted before such signs were present. Palliative treatment of any kind is certainly entirely out of place in those types developing during the pre-adolescent age. The diagnosis would also be hastened if once the disparity and uncertainty existing between the pure posterior and anterior types were recognized. Following operative treatment, x-ray or radium treatment should be used and continued for a considerable length of time. Organotherapy in the form of substitution treatment, using both anterior and posterior lobe preparations, provided both lobes of the pituitary gland have been removed during operation, is indicated. The deficiencies of other ductless glands, the thyroid, the gonad, the adrenal, etc., should be considered and treated if clinical evidence indicates that they are secondarily involved. Should there be any signs of definite recurrence of growth demonstrated by roentgenogram, or presence of intracranial pressure symptoms, secondary operation should be considered.

Prognosis.—The prognosis in these cases, even under the best operative and medical observation, is undoubtedly unfavorable. In the great majority of cases which have been operated on comparatively early there has been undoubted prolongation of life and marked amelioration of symptoms. In some of the cases in which the operation has been done late, after definite hemiopia, choked disks, or partial blindness are present, there has been a restoration of sight and marked amelioration of other intracranial symptoms, such as headache, nausea, vomiting, and general weakness. Organotherapy has undoubtedly helped to restore and to remove a great many of the distant symptoms, such as, for instance, general weakness, polyuria, loss of libido, and changes due to secondary insufficiency of other ductless glands, especially of the thyroid.

Pathology.—The pathology of these cases consists mostly of definite tumefactions of different varieties, usually having their origin in the posterior lobe of the pituitary body. A more detailed consideration of these growths will be given in the following section (page 445). In this case, on account of the absence of an autopsy, no definite pathology can be given, with the exception that there was undoubtedly some rapidly growing tumor present, involving to a large extent the posterior lobe of the pituitary, without the production of a decreased function or secretion of the anterior lobe. There were no other clinical evidences that other ductless glands were decidedly involved. The thyroid was clinically not changed. There were no pigmentations, dermal changes, or marked disturbances of blood-pressure indicating adrenal disturbance. The gonads were certainly *not hypoplastic;* on the contrary, they were developed to the normal size according to the age of the patient. The clinical picture demonstrated direct pressure upon the chiasm and the motor oculi nerves, with some evidence of pressure upon the uncinate gyrus, exhibited by the so-called "fainting spells or epileptiform attacks." Muscle atrophy (dystrophy) was present, probably due to muscle disuse. The long bones were particularly overdeveloped, demonstrating an overactivity of the epiphyseal junctures, very similar to that existing in eunuchs, which is another evidence that the gonads, although well developed, were probably insufficient, or at least that there was probably an insufficiency of the internal secretions produced by the interstitial cells of the testicles, associated with at least normal secretion from the anterior lobe of the pituitary. The extreme length from the symphysis to the soles of the feet, and the extreme span, which is made up entirely of long bones, is merely a disproportion due to the overgrowth of the long bones. The same evidence of this overgrowth of the slender bones is exhibited in this case in the typical eunuchoid hands, which is due to the above two operative factors.

B. Posterior Lobe Insufficiency, Postadolescent Neoplastic Type

Etiology.—As stated under a previous analysis of the symptoms for diagnosis, the association of typhoid with this disease is probably more than a coincidence. There have been many other cases in this series of pituitary disease, which came on immediately following typhoid. Cushing refers to the fact that in his own series as well as in those collected from the literature, typhoid is undoubtedly a predisposing if not an exciting cause of pituitary disease. It is not unlikely that the obesity, frequently following typhoid, may be due to insufficiency of the posterior lobe. The only other possible predisposing cause, in the following case, is trauma, which occurred, however, three years after the onset. Whether it had any effect in reactivating and changing the course of progress of this disease, is uncertain. Its association, however, in this as well as in the other cases of posterior insufficiency, in the pre-adolescent age, coincides with many cases found in the literature, and is probably more than a simple coincidence. In these cases of neoplastic pituitary disease, usually consisting of cystic adenoma or hyperplasia, lues is rarely an etiological factor. As has been stated in the description of Case I, this is not true of those diseases of the pituitary which are not associated with neoplasm of the anterior lobe. The negative Wassermann reaction of the blood and the negative spinal fluid tests help to exclude, but do not entirely negate, the luetic element as a possible cause in this case. The dictum to give antispecific treatment in these neoplastic cases, of course, is not so absolute, although there are a few cases reported, due to gumma of the pituitary body, in which this indication would apply to the neoplastic as well as to the aneoplastic type.

Symptomatology.—History: Case VI.—Mr. H. B. T., aged thirty-five, General No. 1622, St. John's Hospital, St. Louis, referred by Dr. Geo. Sihler, Jr., Litchfield, Ill., March 17, 1917.

Present.—Chief Complaints: (1) *Defective vision,* affecting principally the temporal sides of both visual fields. The loss of vision is more marked in the right eye. The patient is able to read heavy print with the left eye, but is able only to distinguish outlines and forms with the right eye. (2) *Severe headaches,* intermittent, located in the mid-frontal region, localized one inch above the bridge of the nose. This changes to sensation of weight and compression, described as sensation as if a cap were forcibly pulled down about the frontal and temporal regions. (3) Marked *constipation* and *gaseous distention of the abdomen.* (4) *Tenderness, with lancinating pains across the abdomen,* occasionally radiating through the abdomen and into the penis. (5) *Slight thickness of the fingers* and *increase in size of the hands and feet.* The patient does not wear a larger glove but is of the opinion that his shoes were slightly tighter than usual at the last fitting. (6) Marked *tendency to drowsiness and heavy sleep.* (7) *Temporary defective hearing in the right ear,* not present at this time. (8) Marked *diminution in urinary output.*

Duration.—Eight years.

Course.—(*a*) *Onset:* Eight years ago, *following typhoid fever,* the patient had a condition characterized by marked *polyuria, polyphagia* and *polydipsia,* the nycturia reaching eight or nine times during the night. This was associated with rapid, extreme emaciation, progressive anemia, weakness and marked *increase in general nervousness.* The urine was repeatedly examined for sugar and found *negative.* The above group of symptoms continued for three years.

(*b*) *Progress.*—Following this, there was a *remission,* during which time there was *marked improvement* of all symptoms. The patient *gained weight,* the anemia disappeared, and the general condition apparently returned to normal. The patient states that during this time he noted slight *enlargement of the fingers* and *increase in the size of* *the hands and feet.* Six years after the onset of the disease, about two and one-half years previous to the present observation, while the patient was under a severe nervous and mental strain, there occurred the first evidence of a return of symptoms. This began with *severe emotional symptoms,* consisting of *uncontrollable periods of crying.* At this time *extreme drowsiness* and torpidity were first noted. Soon after this the patient began *to sleep continuously for twenty-four hours at a time,* and it required constant effort for him to keep awake. Physical weakness, emaciation and anemia recurred. *Intermittent diarrhea was frequently present* throughout the third period of the course. An *abnormal appetite* developed, but there was no return of polydipsia or polyuria. Two years ago, headache was *first observed.* It was located high in the temporal region, radiating back over the parietal bones to the occipital and upper cervical regions. It was very severe in character, consisting of deep-seated throbbing pain, at times changing into a tearing pain in the vertex of the skull. It was markedly intensified by the use of strychnin, becoming almost unbearable after the exhibition of this drug. Two months after the onset of the headache, the *eye symptoms* commenced. The initial defects of vision began in the left eye, consisting of dimness of vision affecting principally the temporal side. This became progressively worse for a time and then began to improve, the left eye returning almost to normal. Soon after the vision in the left eye reached normal, the right eye began to become defective. This right eye visual defect also occupied the temporal field. Later, both eyes became more or less involved at the same time, and this has progressed to the present time, with fluctuations. At times there has been *almost complete blindness for a short interval,* but at later periods *vision in both eyes would be fairly good.* Red splotches were seen on the white page, before both eyes. During the last few months of the disease the previous attacks of diarrhea *have changed into marked constipation,* with tendency to *gaseous distention* and *abdominal pain,* referred to under Chief Complaints. There has been transient defective hearing in the right ear. Slight *fat padding in the mammary and axillary regions* was noted, but no further increase in size of the hands occurred. One and one-half years previous to observation, or after one year of headache, this symptom disappeared entirely for a number of months. When the headache stopped, there was also disappearance of the fat padding. Eight months ago, under Dr. Sihler's treatment, improvement of vision, decrease in the size of the hands and feet, and in the gaseous distention, and *general improvement in the entire condition were noted.* Seven weeks previous to entrance into the hospital, the third exacerbation occurred. At that time the abdominal symptoms were greatly intensified. The headache returned, but seemed different in character from that previously experienced, and is now described as severe, sharp pain in the midfrontal region above the bridge of the nose, accompanied by unrelievable *pains in the arms and legs.* With the onset of this increase in symptoms, the vision has become much worse and has progressed to the present state.

When improvement takes place in the vision, the patient describes it as a vertical curtain being slowly drawn from the nasal to the temporal sides of the eyes. At present the patient has an abnormal, voracious appetite, without abnormal thirst. *The urine is normal in quantity at the present time.* The tendency to somnolence has returned with the last exacerbation. Two years ago, accompanying the second increase in the severity of the symptoms, the patient noticed a *tendency to deviate to the right when walking* with the eyes closed or when in an intensely bright light. Ataxia was present and has continued to the present time. No signs or symptoms referable to other systems.

Past.—Measles, mumps, whooping cough, *typhoid fever,* malaria. Five years ago the patient was "slugged" with a shot bag, first blow being delivered on the left temporal region, producing *fracture* (?) *of the skull* and another on the right parietal region. There was no period of unconsciousness following this trauma.

Personal.—Drank tea heavily formerly, coffee at the present time, in moderation. Tobacco and alcohol in moderation. Venereal history negative. Appetite good, sleeps well, bowels constipated.

Family.—Father living, aged seventy-three, well. Mother living, aged fifty-three, well. One sister living, well. No family history of liver or kidney trouble, cancer, tuberculosis, goiter, or other hereditary diseases. No other condition similar to patient's in family.

EXAMINATION.—*General.*—Very pale, anemic man, 5 feet and 11 inches (179 cm.) in height, weight 142 pounds. Has decidedly uncertain, toxic gait. Musculature soft, atrophic, pseudo-edematous; skin velvety, thick, elastic, dry; fingers and hands puffy, also arms and legs. Marked absorption of adipose tissue, *skin* seems *loose* and *doughy. Slight puffiness about the eyes.* No distinct pigmentation, very slight yellowish discoloration about the face. No abnormal distribution of hair, none on the chest or above a horizontal line across the symphysis, very slight amount in the axillæ and on the legs and forearms. *Pulse,* low volume and tension, stenotic type. Superficial arteries not visible, difficult to palpate; very few visible veins about the body. No edema, cyanosis, or dyspnea. No abnormal position, gait as mentioned above. Temperament phlegmatic. *Temperature* (three days' observation), *97°-98.2° F.; pulse, 68-85;* respiration, 20-24. *Blood-pressure, systolic 110, diastolic 80,* pulse-pressure 30. Measurements: from head to symphysis, 34 inches (86 cm.); from symphysis to soles of feet, 37 inches (94 cm.); length of humerus, 12½ inches (32 cm.); forearm, 11 inches (28 cm.); femur, 18 inches (46 cm.); lower leg, 17½ inches (44 cm.).

Regional (Positive Physical Signs).—*Head:* Hair of good quality and distribution. Temporal arteries not visible or palpable. During headaches has severe pain over the occiput and temporal regions, both sides. Very slight tenderness to pressure over the left eye. No thickening of the external table of the skull. No tenderness over posterior occipital nerves, supra-orbital region, sinuses, mastoids, or muscle insertions. *Ears:* Air conduction normal, bone conduction normal, Rinne's test negative. (Aids to exclude acoustic tumor.) *Eyes:* (For special report, see that of Dr. Hughes appended.) Pupils equal, right does not react to light, left very slightly. Vision greatly disturbed, patient able to distinguish forms only in right eye. Pupils do not contract to light or to accommodation, convergence very poor. Eye-muscles intact, but it is difficult to get the eyes to follow on account of the poor vision; no lagophthalmus, no protrusion or increased tension of the eyeballs. Scleræ clear, with the exception of dilated peripheral venules. *Nose:* Septum deviated to right, hypertrophy of inferior turbinate on that side. *Mouth:* Some overcrowding and irregularity of teeth in the lower jaw, marked pyorrhea of both gums, teeth show fairly good dentine. Mucous membranes pale, no pigmentations or lesions. Tongue coated, pharynx pale, slightly granular, tonsils not enlarged. *Face:* Negative except for the pallor and slight brownish pigmentation about the angles of the jaw and the neck. Seventh nerve intact. *Neck:* Thyroid not enlarged. Veins very slightly visible, not pulsating, no carotid pulsation. Lymph-nodes not palpable. *Chest:* Fairly well developed, symmetrical, expansion fair, equal. Very slight increase in transmission of tactile fremitus over right upper chest. Percussion note rather short, slightly hyperresonant, equal. Slightly roughened, harsh breathing interscapularly, on the right side, over the third and fourth interspaces. Occasionally subcrepitant, dry râles are heard over this area. No other adventitious sounds, râles, or rubs, heard over the chest, normal transmission of voice and breath sounds. No marked increase of râles on coughing. *Heart:* Apex-beat not visible or palpable in the lying position; in the sitting position, leaning to the left, palpable in the fifth interspace, circumscribed, not heaving. No diastolic shock, thrill, rub, or other impulse palpable over apex-beat, precordia, epigastrium, or sternum. Sounds, apex, muffled, distant, slow, regular, no murmurs. Pulmonic second very slightly accentuated, aortic same, slight accentuation of second sound over the gladiolus. No murmurs, rubs, disassociation, or signs of auricular fibrillation. No abnormalities over the large vessels of the chest or neck. *Abdomen:* Not distended or retracted, equal, symmetrical. Slight tenderness high in the epigastrium, just below the ensiform, localized. Small, localized tender area two fingerbreadths to the right of the navel, at the level of the navel; considerable tenderness over McBurney's point on deep pressure. No increased resistance, rigidity, tumefactions, or dullness, including deep in the flanks. Hernial openings closed. *Spleen:* Not enlarged to palpation or percussion. *Liver:* Dullness four fingerbreadths above the costal arch to the costal arch. Liver palpable on deep inspiration, edge blunt, surface smooth, not tender or pulsating. Gall-bladder region free from tumefaction and tenderness. *Kidneys:* Lower pole of the right kidney just palpable, left not palpable. No tenderness in the kidney regions. *Stomach:* Tympany reaches to the umbilicus. No splashing sound, peristalsis, or tumefaction. Tenderness as noted, two fingerbreadths to right of the umbilicus, and below ensiform, midway from this point, under left costal arch. These points are very hyperesthetic, as great pain being produced by picking up the skin and pinching as by pressing directly toward the abdomen. *Colon:* Cecum and ascending colon not palpable. Tenderness as noted, over McBurney's point. Transverse colon not demonstrable, descending colon and sigmoid contracted, slightly tender. Suprapubic region free from tumefaction and tenderness. *Genitalia:* Negative, except for tenderness of the right testicle. *Testicles and penis normal in size. Rectal:* Very painful to examination, external and internal hemorrhoidal veins enlarged. Prostate very small, seminal vesicles not palpable. *Extremities:* Very wide hips, *girdle obesity absent,* no marked fullness above symphysis. Scars over shins and knees, tibiæ not tender. (Bones in other portions of the body not tender, as clavicle and sternum.) No distinct edema, but marked puffiness of the legs and feet, which does not pit on pressure. Arches low, no distinct drop. *Reflexes:* Babinsky, Chaddock, Oppenheim, Gordon, negative. Achilles and patellars greatly exaggerated. Cremasterics, and pectorals present, abdominals exaggerated. Forearm, radio-ulnar, biceps, triceps, greatly increased. Chvostek and jaw-jerk present.

LABORATORY FINDINGS.—*Urine.*—(*a*) Single specimen, yellow, reaction acid. Albumin, dextrose, erythrocytes and casts negative. Few leukocytes.

(*b*) Twenty-four-hour specimen, 1,300 c.c., yellow, reaction acid, specific gravity 1.010. Albumin a trace, few leukocytes. Dextrose, erythrocytes and casts negative.

(*c*) Twenty-four-hour specimen, pale, reaction acid, 2,000 c.c., specific gravity 1.010. Albumin, dextrose, casts, leukocytes and erythrocytes negative.

Feces.—(Two specimens). Brown, formed. Ova, parasites, pus, and mucus negative. Occult blood positive.

Blood:

Erythrocytes	4,000,000
Leukocytes	8,400
Hemoglobin	82 per cent.
Wassermann	negative
Differential count:	
Number of cells counted	100 per cent.
Lymphocytes, small	23 " "
Lymphocytes, large	10 " "
Large mononuclears	3 " "
Polynuclears	60 " "
Polymorphonuclears	3 " "
Mast-cells	1 " "

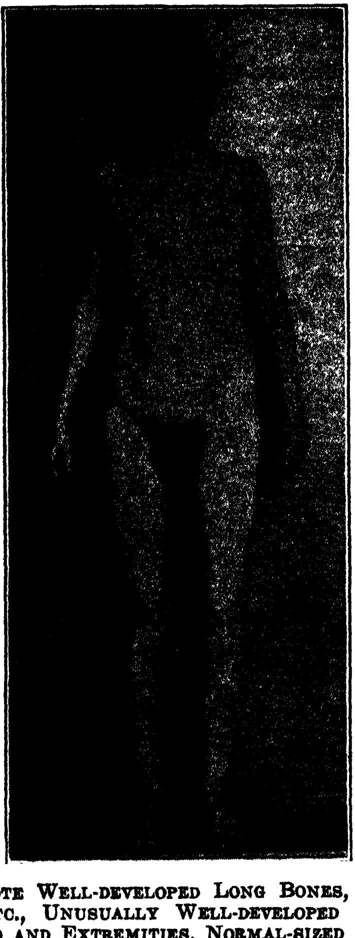
Sugar Tolerance Test (Blood-sugar):

(*a*) (In morning before breakfast)	0.096
(*b*) (After 100 grams ($3\frac{1}{2}$ ounces) dextrose with 24-hour general diet, and 1 c.c. of 1/1000 adrenalin intramuscularly)	0.080

Spinal Fluid:

White-cell count	3
Wassermann	*negative*

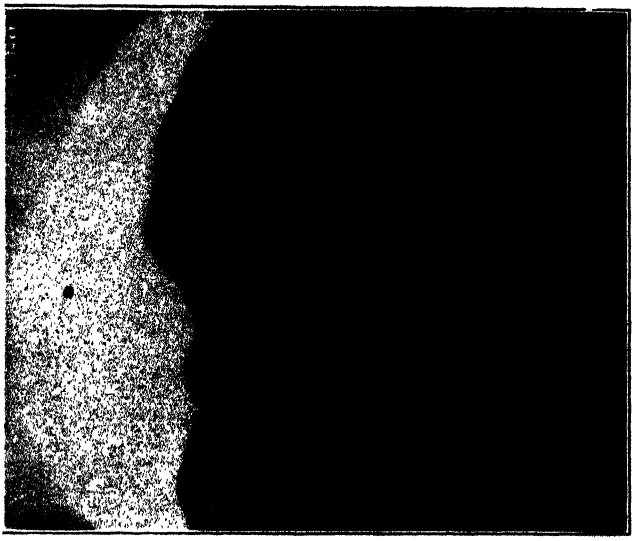
Special Examinations.—*Roentgenogram* (Transverse View of Head —Fig. 2).—Sella turcica greatly enlarged, through anterior-posterior diameter measures 1 inch (2.5 cm.), through vertical diameter measures ¾ inch (1.8 cm.). Normal anterior-posterior diameter is ⅜-½ inch (0.92-1.2 cm.), normal vertical diameter is ⅜ inch (0.92 cm.). Posterior clinoid process almost entirely absent, so that there is a large cavity merging with the mastoid cells. Sphenoid sinus, which is just anterior



CASE VI. Fig. 1.—Note Well-developed Long Bones, Absence of Adiposity, Girdle Obesity, etc., Unusually Well-developed Genitalia, Absence of Hirsuties on Torso and Extremities, Normal-sized Head, Hands, and Feet and Unchanged Nose and Chin, Narrow Hips, and Genu Valgum. (Above figure unchanged by operation.)

and beneath the sella turcica, is almost obliterated, posterior wall of sphenoid being pushed forward and downward. There is a large dark area above and posterior to the sella turcica, measuring two inches in length and one and one-half inches in height.

Perimeter Examination (Dr. H. S. Hughes, 1915, soon after the onset of visual signs).—Bilateral homonymous hemianopsia present. At the time of this examination, the right side of both visual fields was almost completely blind. This blindness did not project into the left visual field, but was limited by a vertical line drawn through the perimeter at its center. There was no inversion of the color fields in either eye. Pupils were equal and reacted to light and accommodation. No disturbances of the innervation of the eyeballs or lids.



CASE VI. FIG. 2.—(ONE MONTH PREVIOUS TO OPERATION.) NOTE LARGE SELLA TURCICA, ANTEROPOSTERIOR DIAMETER, 25 cm. (Normal 10 to 14 cm.), DEPTH 18 cm. (Normal 8 to 10 cm.); ANTERIOR WALL PROJECTING INTO SPHENOIDAL SINUS; AND POSTERIOR CLINOID PROCESS ALMOST OBLITERATED. OTHER MARKINGS NORMAL.

SUBSEQUENT COURSE OF CASE

Report of Operation, by Dr. Allen B. Kanavel, Chicago, Illinois.

"APRIL 26, 1917.

"I operated upon the patient and came down upon a mass in the neighborhood of the hypophysis which I suppose came from the hypophysis itself, but that is of course impossible to say. We scraped out a fair amount of the mass. A large amount of fluid escaped, so evidently it is more or less cystic, but there seemed to be proliferating tissue in addition to the cyst.

"I must say that I am rather dubious as to the ultimate outcome, since it seemed to me that the peduncles are involved and possibly the tumor has grown into the brain-tissue, in which case the operation should be considered nothing more than a decompression rather than a curettage.

"I have had several cases in which I have been able to secure very satisfactory results, where the peduncles have not been involved. Where there is destruction of the sella turcica rather than an enlargement, the results have as a rule not been the best.

"He has a temperature to-day of 101°, has no evidence of complications, and seems to be in good condition.

ALLEN B. KANAVEL."

"APRIL 30, 1917.

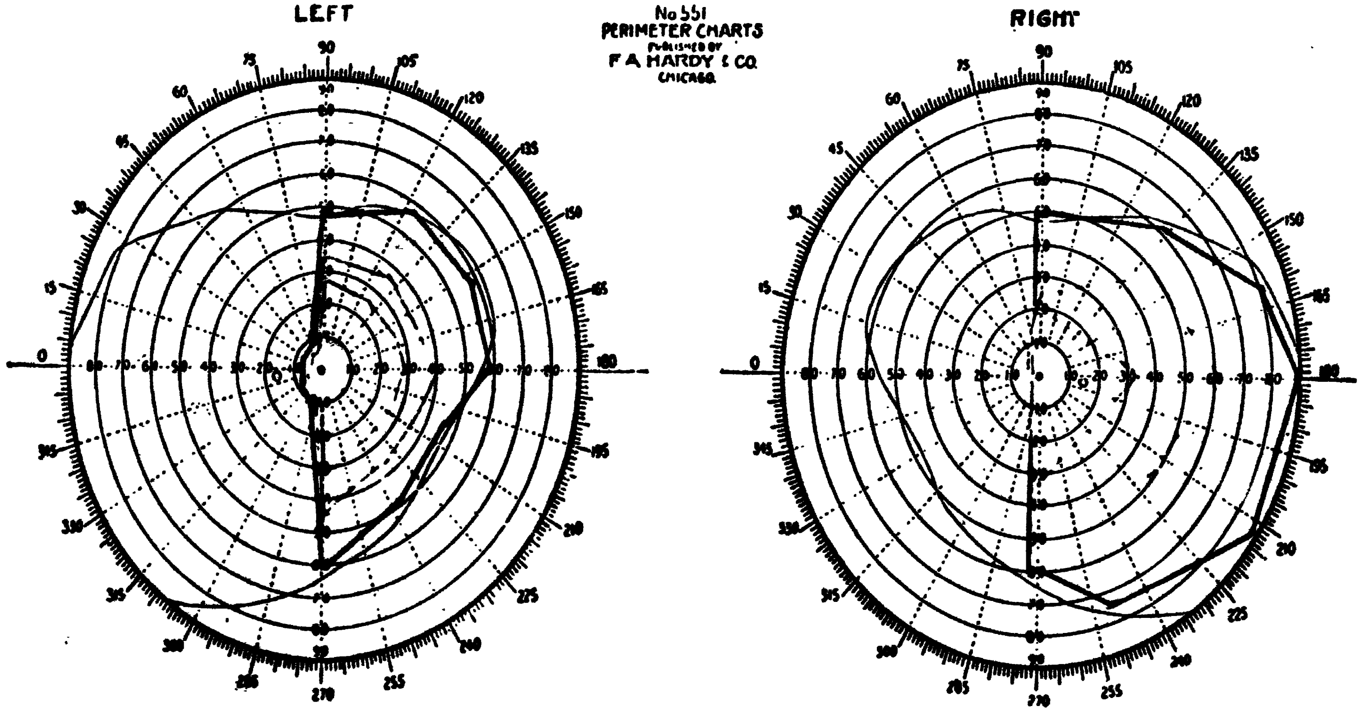
"I thought you would like to know that your patient with the hypophyseal tumor has made a very satisfactory recovery and will go home within a few days. I believe there is some slight improvement in sight. He is able to recognize fingers, which he was not able to do at the time of examining him before the operation. It is probably too early to estimate the maximum amount of improvement that he will secure, but owing to the extensive atrophy in the eyes, naturally we cannot expect a great deal. He is now sitting up, and as far as I can see will make complete recovery as far as his general health is concerned. As regards the pressure upon the peduncles, he still has evidence of that, but this also I think might be present, even though the pressure were relieved. Therefore I have asked him to return to me within the next three months for examination, at which time I shall be glad to let you know how he is getting along.

ALLEN B. KANAVEL."

Re-admittance Observations (May 7-10, 1918)

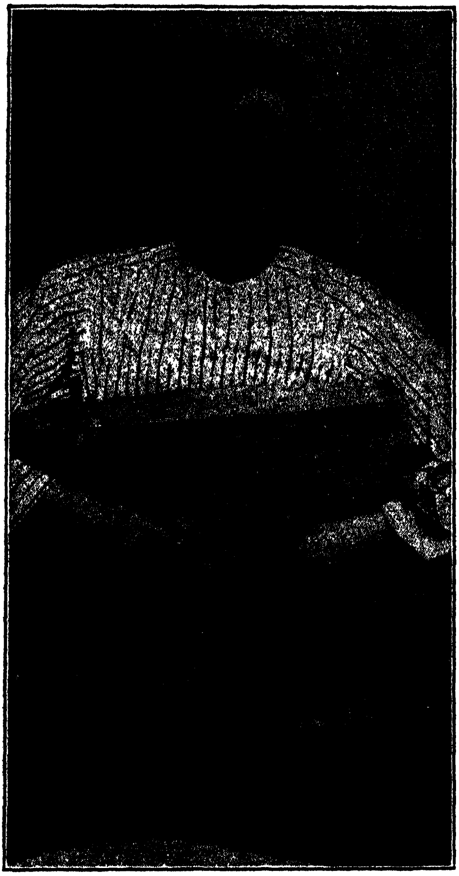
HISTORY: *Present.*—(*a*) *Chief Complaints.*—(1) *Blindness,* especially of the right eye, less marked in the left; (2) *headache,* involving particularly the right cranium; (3) *loss of weight,* 35 pounds since operation.

(*b*) *Course.*—On April 26, 1917, the patient was operated upon by Dr. Allen B. Kanavel, of Wesley Memorial Hospital, Chicago. The patient showed signs of improvement, but was extremely weak for one or two months following the operation. This weakness disappeared, and the symptoms of which he had previously complained were improved. For two months, the polyuria was absent and his condition in that respect was normal; then the patient *again developed a polyuria,* which lasted for three months. During this time the urine was examined frequently, but at no time was there found any trace of sugar. After this the polyuria disappeared and the urine has been normal in amount. The slight swelling of the hands and feet also returned to normal. Previous to the operation, the bones had appeared to be enlarged, but now



CASE VI. FIG. 3.—PERIMETER CHART. BILATERAL HOMONYMOUS HEMIANOPSIA. (See report of Dr. H. S. Hughes.)

seem normal. The patient wears the same size of shoe and glove as previously, but they are much looser. The pains in the arms and legs have not entirely disappeared, but are less severe. Before operation, the patient had noticed subjective vibration of the eyeball. He had never been told by any one that this could be noticed. On account of this vibration, he would go about with eyes closed, as this sensation was absent when the lids were not open. This condition lasted for some time after the operation, but has since disappeared and has not recurred. The sight became improved after two months, and continued to improve for six months. The patient was able to distinguish objects, as the rung of a chair, or, in walking, the sidewalk; and if he knew a person, he was able to recognize him. He could also read the headlines of a newspaper. At the present time, however, he is able only to



CASE VI. FIG. 4.—(ONE YEAR FOLLOWING OPERATION.) NOTE NORMAL-SIZED HANDS, WITH TENDENCY TO TAPERING OF PHALANGES, ABSENCE OF PADDING ON BACKS OF HANDS, ABSENCE OF CHANGES OF ACRAL BONES OF HEAD, SLIGHT STRABISMUS, AND INVISIBLE OPERATIVE SCAR ACROSS SUPERIOR MAXILLA.

distinguish light from darkness with the right eye, and with the left is able to distinguish objects. At one time during the summer following operation, he was able to tell the color of a house some distance away. At present the headaches are less severe, involving the right side, beginning either posterior to the right mastoid process or in the right frontal region, and tend to respond more readily to treatment. Recently the headache has had greater tendency to originate in the right frontal region. It has very seldom occurred on the left side. The patient was free from these headaches until six months ago, when he contracted a cold, which remained practically the entire winter; while he was suffering from this cold, all symptoms tended to recur, but with less severity than previous to the operation. Before the operation, the patient was a great meat-eater and could not eat cakes, pies, etc., but at the present time he has a desire for fruits rather than for meats. He has noticed during the past three months that the headaches have come on after eating. His appetite is ravenous, *but the patient has lost about 35 pounds in weight since the operation.* In December, 1917, the patient returned to Chicago to consult Dr. Kanavel, who noticed pads of fat under both arms. The patient was then placed upon pituitary gland, three times a day, by mouth, and under this treatment the fat pads disappeared. Ataxia has also disappeared.

EXAMINATION.—*General.*—Tall, slender, eunuchoid type of individual. Color is a pure pallor, *very slight pigmentation present about the forehead and angles of the jaw,* extending a few inches over the cervical region. *Skin moist, velvety, soft; subdermal tissue thick, pseudo-edematous. No girdle or mons obesity.* No abnormal distribution of hair, slight amount under the arms, on the face, and on the mons, no hair on the trunk or extremities. *Genitalia well developed,* testicles measure 2 inches (5.08 cm.) in length, and ¾ inch (1.8 cm.) in breadth; penis unerected, 4½ inches (11.2 cm.) long. No cyanosis, dyspnea, or edema. No abnormal gait, except marked staggering, probably due to blindness; no abnormal position. *Pulse, slow,* regular, equal, symmetrical, low volume. (Three days' observation.) *Temperature, 97.6°-99° F.* (36.4°-37.2° C.) *pulse, 80-88. Blood-pressure, systolic 110, diastolic 75.*

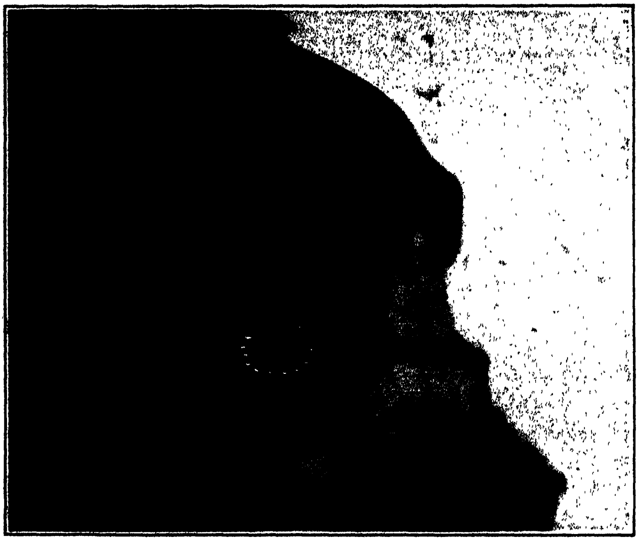
Regional.—No marked changes from the previous examination recorded above. Perfect, almost invisible postoperative scar extending halfway to the eye on each side of the nose.

LABORATORY FINDINGS.—No changes except sugar tolerance test as given below:

Chemical Blood Analysis:

(*a*)	Blood-sugar (5-8-18)	0.076
(*b*)	Blood-sugar (5-9-18) following 300 grams (10½ ounces) dextrose, given in 24 hours, by mouth, and two injections of adrenalin, 8 minims (0.5 c.c.)	0.080

SPECIAL EXAMINATIONS.—*Roentgenogram of Skull* (Transverse View).—Antrum, frontal sinus, and nasal processes have been very slightly disturbed by operation. Sphenoidal sinus, anterior and posterior walls, easily defined. The entire sinus is much clearer, less evidence of compression posteriorly than previous to operation, as shown in the roentgenogram at that time. Posterior clinoid process entirely absent, so that there is almost a straight line going from the anterior wall of the sella turcica back to the mastoid cells above the aural canal. No changes in other details of the skull.



CASE VI. FIG. 5.—(ONE YEAR FOLLOWING OPERATION.) NOTE UNCHANGED RADIOGRAPHIC FINDINGS AS COMPARED WITH ROENTGENOGRAM PREVIOUS TO OPERATION. SELLA TURCICA HAS SAME MARKINGS AS IN FIG. 2. ANTERIOR WALL OF SELLA TURCICA NOT QUITE SO CLEAR-CUT AS IN ROENTGENOGRAM BEFORE OPERATION.

Diagnosis: *Hypopituitarism, Posterior Lobe Insufficiency, Occurring after Adolescence, Associated with Neoplasm of the Pituitary Gland.*—This diagnosis is based upon the points of diagnostic importance supplied by the *clinical history,* beginning with *polyphagia, polyuria,* and *polydipsia, associated with* extreme, marked *emaciation* and *progressive nervousness.* The *initial glycosuria, usually present* in this type of case, was *not* found during the numerous examinations of the urine, possibly due to the urine analysis not being made at the very onset of the disease. During the first period of the course of the disease there must have been a *hyperfunction* or *oversecretion* of the *posterior lobe* of the hypophysis. At about the end of the third year the polyuria ceased, coincident with apparent improvement of the patient. It will be noted that there was a *gain of weight* during the second three years. During this same period of obesity, it is also stated, there was an *increase in the size of the hands and feet.* It is very evident that there must have been a decided change in function of the posterior lobe, to explain the second three years of the course of this disease. In fact, it is very evident that the early overactivity of the posterior lobe changed decidedly into a hypo-activity of this lobe, producing a return to the normal amount of urine and the addition of adiposity. This was associated to a slight degree with a hyperactivity of the anterior lobe, demonstrated by the slight *increase in the size of the hands and feet.* The third stage, during the last two years' illness, was marked by severe nervousness and mental disturbances, such as uncontrollable periods of crying. Another marked nervous symptom was the heavy and prolonged sleep, the patient being able to sleep for twenty-four hours at a time, and being awakened with difficulty. The urine remained normal in quantity during the third stage of the disease up to the time of observation, when it was decreased in amount. Ataxia was a symptom of later occurrence, probably indicating pressure upon the cerebral peduncles. These later signs, particularly the drowsiness, the anuria, and the retrogression of obesity, indicate a continuation of depression of the secretions of the posterior lobe, without additional evidence of hyperactivity of the anterior lobe.

The subsequent course of this case following the operation, at which time a large portion of the glandular tissue was removed, is interesting. During this operation it is more than probable that a portion of the anterior lobe was removed, and we know, from the previous hormonic signs, that the posterior lobe had changed from a hyper- to a hypoactivity. *Yet there was no marked adiposity;* in fact, there was *a loss of 35 pounds in weight,* which should *not* follow a more decided deficiency of the posterior lobe. Nor were there retrogressive changes in the genitalia, which would be expected from additional insufficiency of the anterior lobe. Dr. Kanavel undoubtedly was seeking the advent and development of the adiposity, as is proved by the patient's statement that during a careful examination made by him six months after operation, special mention was made of the axillary obesity. At the readmittance examination in the hospital there was no evidence of a decided girdle or mons obesity over that which had been observed at the previous examination before removal of the growth. *The reason for the absence of obesity, which should occur with insufficiency of the posterior lobe in this case* and which does occur in those cases of bilobar insufficiency involving both the anterior and the posterior lobes of the hypophysis primarily, *has never been convincingly explained.* As the experience of the writers increases and more and more cases in the literature are analyzed, it is their belief that in these secondary hyposecretions of the posterior lobe this absence of girdle obesity is a constant hormonic sign, *i. e.,* that *this absence of obesity is constant in both the pre- and the postadolescent types of the hyposecretions of the posterior lobe which have been preceded by a hyper- or overactivity of this lobe.* If this is true, it will be seen that the characteristic *girdle and mons obesity is not a hormonic sign of the hyposecretion of the posterior lobe which has followed, or is secondary to, a hypersecretion* *of this lobe,* while, on the other hand, this same obesity is a constant sign in those cases which have begun primarily as a hyposecretion of the posterior lobe. The additional reason why this same adiposity is present in one instance and absent in another, with the same deficiency of secretion of the posterior lobe, probably lies in the effect of other internal secretions which have undergone decided changes during the hyperactive stage of the posterior lobe during the first few years of the course of the disease. These changes in other ductless glands are probably entirely different in those primary hyposecretions of the posterior lobe having the classical hormonic signs of obesity associated with the insufficiency of this lobe of the hypophysis.

A more careful examination of the *testicles,* as noted in the above report, demonstrated that they were *practically of the normal size.* There were *no retrogressive changes in the penis* as compared with the previous examination. The small enlargement of the hands, fingers, and feet, which the patient's early history related, was supposed to have been reduced to normal. This is very unlikely, for the reason that these structural changes in the bones are retained to a considerable extent after the activity of the anterior lobe is changed into the opposite degree of function and secretion. The *slight tapering of the fingers* from the second phalangeal joint to the tip, which the writers have noted in a number of cases in which favorable results have been accomplished upon anterior lobe hypersecretions, following either operation or the administration of glandular products, is important. The postoperative history notes the recurrence of the polyuria for three months following the operation, a sequence which has been noted by Cushing and others following operations upon hyposecretions involving the posterior lobe. Cushing and Aschner also noted the temporary increase of libido occurring a short time after these operations. This is due probably to a transient stimulation of the secretions of the anterior lobe of the pituitary from the relief of pressure or other influence upon it, occurring a short time following operation.

The *evidence of localized intracranial pressure,* derived from the history of pituitary neoplasm, appeared during the sixth year of this disease, or two years previous to observation. At that time a *very severe headache* commenced. Two months later the first *defect of vision* was noted, consisting of dimness of vision affecting principally the temporal side of one eye. This disturbance of vision gradually became worse for a time and then apparently disappeared almost entirely. Later it returned, affecting the vision of the left eye. This then disappeared, and the right eye again became involved. Finally there was a hemianopsia affecting the temporal fields of both eyes. The patient describes these changes, "as if a curtain were drawn vertically before the eyes." This constant, fleeting, transient blindness led an oculist under whose observation the patient was during the early course of these changes, to make the diagnosis of toxic amblyopia. Emphasis at this point on the very *marked deviation from the typical temporal bilateral hemianopsia* which is usually assigned to diseases of the pituitary producing pressure upon the chiasm, is thought opportune. It is probably true that the *great majority* of the cases of diseases of the pituitary gland *do not have any disturbance of vision* on account of *not* being due to neoplasm of the hypophysis. Those which have neoplastic enlargement of this gland *do not have this classical blindness constantly limited to the temporal sides* of the perimeter field, as frequently described. This is due to the fact that in the neoplastic type there is not an even, symmetrical pressure upon the chiasm which supplies the nasal side of the retina. This pressure is directed first upon one side, later upon the other, and if the tumor grows rapidly it frequently decompresses itself into the sphenoidal sinus, which for a certain length of time relieves the pressure upon the chiasm entirely and may allow in this way a temporary return to normal vision. As shown by the roentgenogram, this is what occurred in this case. It is noted in the history that strychnin, which was given probably as a diffusible stimulant, had the very decided effect of increasing the headaches.

There was considerable relief from the intracranial pressure symptoms for some time subsequent to the operation. The reëxamination, over a year following operation, demonstrated that there was still considerable headache, of less severity, and that the eye signs had returned to almost the complete degree of blindness which had been present previous to operation. This of course was to be expected, on account of the presence of the optic atrophy previous to surgical interference. It is also probable that there has been a return of the growth of the neoplasm following operation, which would counteract any relief from pressure obtained by this procedure.

Another very interesting phenomenon which is noted in the history, as well as in a considerable percentage of our other observations of pituitary cases, is the *obstinate constipation,* the *gaseous distention,* and the *abdominal pain* located in the lower portion of the abdomen. Knowing the control of the posterior lobe of the pituitary over the contraction of involuntary muscles, it may be assumed that during the early portion of the course of this disease there was a hyperstimulation of the circular muscles of the large intestine, which might be accountable for the constipation (spasticity of the colon) and also the gaseous distention. Later it is noted that during the hyposecretion of this lobe of the pituitary, there was present a *diarrhea.* Whether this was due to the opposite effect or whether it was merely an associated condition from an entirely different source than the pituitary secretion, can be only surmised. The amount of *abdominal pain* present in this case requires special mention on account of the many cases present in the series to be reported which have had such prolonged and severe pains in the lower portion of the abdomen as to be mistaken for surgical diseases. The first diagnosis made is usually that of appendicitis, and the patient is appendectomized, without relief. On the contrary, additional pain occurs, and a second operation is usually performed for postoperative adhesions. One patient, under observation at the present time, to be reported later in this series, has had three operations, without any amelioration of symptoms. During two operations, the appendix, a tube and an ovary on the right side were removed, with the result of only more continuous and severe abdominal symptoms in this portion of the abdomen. *The pain in the extremities and the rest of the body,* present in this case, is another symptom which has been reported in many cases in the literature. This is another symptom very rarely connected with the pituitary gland.

The PHYSICAL SIGNS of importance in this case are directed toward the hormonic effects of (1) the early hypersecretion of the posterior lobe, with slight increased secretion of the anterior lobe, which were followed by (2) hormonic signs indicating, *at the time of observation,* an insufficiency of the posterior lobe, without much evidence of implication of the anterior lobe as being either overactive or inactive. The local intracranial pressure signs have been spoken of above in the paragraph summarizing the evidence in the history referring to the headache and ocular disturbances. It is unnecessary to add more than will be found under Special Examinations—the radiographic evidence of an enlarged sella turcica, in which the posterior clinoidal process of the sella turcica had been destroyed and the anterior wall had been depressed into the sphenoidal sinus, producing a much enlarged cavity containing, as was proved at operation, a large cystic neoplasm. The hormonic signs, or those physical changes in other structures of the body due to the posterior lobe disfunction, are as follows: (A) The rapid and *progressive emaciation,* associated with early *polydipsia* and *polyuria.* This rapid absorption of adipose tissue is characteristic of *excessive function* of the *posterior lobe.* There is slight indication that this early hypersecretion of this lobe produced some inactivity of the interstitial function of the gonads, by the evidence of a *slight padding above the mons and slight fullness of the mammary glands. The long bones were unusually well developed,* but whether or not there was unusual growth of these bones during the first three years of the course of the disease is uncertain. The inhibition (?) of the gonads, which, as stated before, would tend to delay the closing of the epiphyseal junctures, co-existent with a normal exciting hormone from the anterior lobe, would be inclined at least to produce a normal length of the long bones. (B) The physical *signs* further indicate a *change to hypoactivity of the posterior lobe occurring during the second three years of the course* of the disease. This obesity was later reduced to a state of emaciation, present during the observation, and, according to the history, during the two previous years. This absence of obesity, in this as well as in other cases to which personal reference is made in the classical type of posterior lobe insufficiency, has, as far as the writers know, no definite explanation except that it is due to secondary disturbances of other ductless glands. Late in the course of this disease there was *slight padding and thickening of the subcutaneous tissue,* producing obesity *about the entire body,* with secondary dermal changes. These signs are probably due to secondary insufficiency of the *thyroid gland,* frequently accompanying, as a late complication, insufficiency of both the posterior and the anterior lobes of the pituitary. The decided somnolence, stupor or drowsiness might also be attributed to a certain extent to this secondary hypothyroidism. The writers have noted this in a number of bilobar insufficiencies of the pituitary, occurring late in the course of the disease. The infiltration of the subdermal tissue and the skin changes, associated with the extreme drowsiness and somnolence, have been proved, in other cases, to be due to hypothyroidism, by the fact that both these physical signs and the somnolence have been relieved by the exhibition of thyroid gland. The *low blood-pressure* (systolic 110, diastolic 80), the *slow pulse,* and the *subnormal temperature* are other physical evidence that there was, *at the time of observation,* a *hyposecretion* of the *posterior lobe* of the hypophysis.

THE LABORATORY TESTS all indicate a *hypopituitarism.* The twenty-four-hour total amount of urine passed during observation varied from 1,300 to 2,000 c.c. The specific gravity was almost constantly 1.010. There were no other abnormalities except an occasional trace of albumin. The sugar tolerance test demonstrated that the blood-sugar dropped from 0.096 to 0.080 following the ingestion of 100 grams (3½ ounces) of dextrose (adrenalin 1/1000, 10 minims, given hypodermatically during the time the dextrose was taken by mouth). Personal observations have noted that in many of these cases the *blood-sugar actually decreased in amount following the ingestion of the dextrose* given for these tests in hypopituitarism, *i. e.,* that the amount of blood-sugar is smaller *following the twenty-four-hour ingestion of dextrose* (during which time one injection of adrenalin is given) than it was previous to taking these various amounts—100 to 400 grams (3½ to 14 ounces)—of dextrose. This has been observed more constantly in the hypopituitarisms than in hyposecretions of other ductless glands, such as the thyroid, in which the same tests were made. The blood examination was practically within the normal, and mention is made that eosinophilia, so frequently referred to in the literature as being present in these cases, has not been found in our series of cases. A great majority of them have shown the usual increase in lymphocytosis. The feces analysis was negative. Special examinations included only the roentgenogram (Figs. 2 and 5), which explains itself, showing an unusually large sella turcica, and the perimeter examination (Dr. Hughes), showing a bilateral *homonymous* hemianopsia. It will be remembered that the history describes the fleeting location of these blind fields, depending upon localized pressure upon the optic nerves.

Complications.—The complications in this particular case might be divided into (1) those referring directly to the pressure from the pituitary neoplasm itself, and (2) those involving other organs of the body and the ductless glands, exerted through its hormonic effects. The clinical as well as the operative evidences, and the postoperative signs and results, all prove conclusively that this cystic neoplasm of the posterior lobe decompressed itself anteriorly, through the posterior wall of the sphenoidal bone of the skull, and also posteriorly, to such an extent as to produce necrosis of the posterior clinoid process. There is no clinical evidence indicating pressure upon the uncinate gyrus. There must have been pressure upon the peduncles of the cerebellum, causing ataxia. There was no clinical evidence of hydrocephalus. Pressure upon the chiasm and other intracranial nerves has been mentioned elsewhere. The secondary involvement of the thyroid gland was suspected from the subdermal and dermal changes and the somnolence, and the possible secondary involvement of the cortex of the suprarenal, possibly producing the slight pigmentation or other complications. If this case is accepted as one of pure posterior lobe insufficiency, the slight stage of anterior lobe overactivity present during the second three years of the course of this disease might also be given as one of the complications. The hemianopsia and optic atrophy in this case need no special reference. The very interesting clinical symptoms referable to the gastro-intestinal tract and the abdomen, occurring in this case, should be given more thought and consideration in abdominal diagnosis. Their exact explanation as yet is indefinite. That they have to do with the secretions from this lobe, affecting the involuntary muscular contraction of the intestine and, in the female, the uterus and the interstitial substance of the ovaries, is more than likely. Possibly the "neuralgia of the ovaries," designated by older writers and practitioners, really has some basis as an explanation for the abdominal pains associated with pituitary disease occurring in females. It is true that at operation there are no macroscopic changes found in the ovaries in these individuals, yet in a number of cases in which Cushing and others removed parts of the tissue of the testicles in the males, it was shown that there was almost complete hypoplasia of the tissue of Leydig, although the size of the testicle and its macroscopic appearance were normal.

Sequelæ.—The sequelæ of these diseases of the insufficient variety *associated with neoplasm,* are not important, because of the fact that they are usually the terminal states. In those varieties, however, commencing as a hyperpituitarism *not having neoplasm* as a basis for disturbances of function, the sequelæ are usually diseases of other ductless glands or later inactivity of this same lobe of the gland. It is very rarely that we note, in the pure posterior lobar types having underactivity of this gland, a development in the opposite function of overactivity. This undoubtedly occurs in the *pure primary hyposecretions* of the anterior lobe of the pituitary. One frequently sees an individual of *markedly arrested skeletal growth,* undoubtedly due to insufficiency of the anterior lobe of the pituitary gland during pre-adolescent life, who afterward developed into a typical acromegalic type of individual having rapidly growing and enlarged acral bones and definite evidence of hyperactivity of this lobe. The sequela connected with other ductless glandular anomalies has been given under the complications. This dyscrasia, associated with the insufficiency of the thyroid, occurring later in the course of these diseases, has been found to be not infrequent.

Association of Other Diseases.—The association of this individual case with *typhoid fever is significant.* The history states that this condition of unusual hyperactivity of the posterior lobe came on soon after a typhoid infection. The writers have noted this association in many other cases. The *obesity frequently following typhoid has been known even by the laymen.* No reference is made of its connection with pituitary disease in the medical text. The association of posterior lobe disturbances with trauma has been well known, and this history occurs in the above case, although, as has been stated, trauma resulting in skull fracture (?) was present in this case three years after the onset of the condition.

Clinical Varieties.—From the preliminary discussion of the hormonic signs referable to the different activities of each lobe of the pituitary gland, sufficient basis should be offered for more clear-cut differentiation, and hence, classification of these cases, than exists in the literature at the present time. A detailed discussion of these signs referable to both over- and underactivity of the *anterior lobe* was given in the initial section of this series. Following this, the different classical varieties of anterior lobe insufficiency occurring at different ages and presenting different clinical complexes were reported in detail. In Section 4, an analysis was made of the hormonic signs of the *posterior lobe,* including those due to its overactivity, as contrasted with those due to the deficiency of this lobe. In order to further differentiate the clinical complexes presented by diseases of the anterior and the posterior lobes, this place has been selected to compare the *hyposecretions of these two lobes,* as shown in Table 4.

It will be noted from the following table that the most important clinical evidence indicative of decreased secretion of the posterior lobe of the hypophysis is the negative intestinal pituitrin reaction and the decreased metabolism, producing adiposity and an unusual tolerance for carbohydrates. The decided classical girdle, mons, and mammary obesity, the presence of an increased sugar tolerance (as is evidenced by the absence of glycosuria or increased blood-sugar following the ingestion of unusual amounts of dextrose), and the absence of an increased amount of carbon dioxid in alveolar air, with the secondary involvement of other ductless glands, particularly those concerned in regulating the metabolism, are the most important positive hormonic signs of the posterior lobe. It will also be noted that there is negative evidence referable to the osseous and the genital systems, and absence of changes in the blood-pressure or the urinary output. The slow pulse and the subnormal temperature may be present in hyposecretions of either the anterior or the posterior lobe. They have been found by the writers, however, to be most distinctive of posterior lobe insufficiency. Other clinical manifestations which are classifying factors in pure posterior lobe diseases of the hypophysis pertain (1) to the activity of the lobe, and (2) in the neoplastic type, to the different kinds of tumors producing this lesion. Those differential points dealing with the hormonic signs denoting different degrees of activity have been given in detail in Sections 1 and 4.

Treatment.—The treatment in this type of hypopituitarism does not differ from the case of similar type occurring in pre-adolescent life, described previously in this section (Case V). These cases should be treated, of course, on the basis of pituitary neoplasm, using the secondary signs produced by the hormonic effects of the secretions as early diagnostic evidence. It is unnecessary to repeat again that early **operation,** trans-sphenoidal decompression or transtemporal removal of a large portion of the growth, is the prime indication. This should be done, as previously stated, before there is marked evidence of pressure upon the chiasm or other intracranial structures. Postoperative treatment should consist of **massive** x-ray or **radium exposures,** combined with **substitution glandular therapy.** Glandular therapy should consist of both lobes of the gland, but particularly the posterior, given in sufficiently large doses, by mouth and hypodermatically, to restore the normal sugar tolerance. These cases should be kept constantly under prolonged observation. The postoperative treatment differs very little from that of primary growth and its sequences.

TABLE 4.—HYPOPITUITARISM

	Anterior Lobe	Posterior Lobe
A. OSSEOUS SYSTEM.	A. *Undergrowth.* 1. (Pre-adolescent) entire skeleton. 2. (Postadolescent) acral, flat and short bones.	A. *Normal.*
B. GENITAL SYSTEM.	B. *Hypoplastic.*	B. *Normal.*
1. Menses.	1. Amenorrhea, metrorrhagia, and dysmenorrhea.	1. Normal.
2. Sexuality	2. Loss of libido, impotence and frigidity.	2. Normal.
C. METABOLISM.	C. *Normal.*	C. *Decidedly decreased.*
1. Adiposity.	1. Absent.	1. Obesity, girdle, mons, and mammary, marked.
2. Sugar tolerance.	2. Normal. Hyperglycemia rapidly produced by ingestion of 1.59 grams of dextrose per kgm. of body weight.	2. Increased. Glycosuria and hyperglycemia absent after ingestion of 1.59 grams of dextrose per kgm. of body weight.
3. Carbon dioxid in alveolar air.	3. Normal.	3. Decreased.
D. INVOLUNTARY MUSCLE CONTRACTION.	D. *Absent.*	D. Intestinal reaction difficult to produce by large dose, more than 15 minims of pituitrin (O)
E. BLOOD-PRESSURE.	E. *Normal.*	E. *Decreased.*
1. Renal polyuria.	1. Normal.	1. Decreased.
F. OTHER ENDOCRINE GLANDS.	F. *Rarely involved.*	F. Frequently affected, especially thyroid, thymus, and adrenal.
G. TEMPERATURE.	G. *Decreased.*	G. *Decreased.*
H. PULSE.	H. *Slow.*	H. *Slow.*

Prognosis.—The prognosis in these postadolescent posterior pituitary tumors is the same as that occurring in the pre-adolescent age.

It depends mostly upon the early and initial surgical treatment, as previously stated. Even with this, combined with the most careful postoperative care and observation, the prognosis must necessarily be unfavorable as to absolute cure. It is undoubtedly favorable for the relief of the very distressing symptoms due to intracranial pressure and its effect upon the local structures in the neighborhood of the hypophysis.

Pathology.—The pathology consisted of a neoplastic cystic tumor of unknown origin and structure. The neoplastic variety of pituitary disease is one which has gained a great deal of distinction owing to the earlier conception that *all diseases* of the pituitary gland were due to malignant changes of the hypophysis. Foreign writers particularly have dilated upon this point, and from references in the foreign literature it will be seen that hypophyseal tumor has been the common conception of the etiology of secretory disturbances of this gland. It is now well known, and probably true, that the neoplastic variety of diseases of the pituitary gland are probably very much in the minority, and in the writers' experience only a very small percentage of the cases have a neoplastic etiology for secretory disease of the hypophysis. Cushing summarizes the grouping of these tumors as follows:

> "Various classifications of hypophyseal growths have been made by Creutzfeldt (1901), by Courtellemont (1911), by Roussy and Clunet (1911) and by others. Courtellemont, for example, divides them into three groups: (*a*) the epithelial tumors, with which he includes not only the heteroplastic growths with a pavement type of epithelium, but also the various adenomatous strumas which originate from the gland itself; (*b*) non-epithelial tumors; and (*c*) specific tuberculous or luetic lesions.
>
> "Creutzfeldt has shown that out of 55 cases of tumor *without* acromegaly, 34 per cent. were growths from a craniopharyngeal anlage, whereas of the cases of tumor *with* acromegaly, 82 per cent. were homoplastic growths, *i.e.*, adenomas, strumas, etc., of the gland itself.
>
> "In 97 cases collected from the literature by Frankl-Hochwart, the tumor was described in 13 as a carcinoma (7 of them originating from an epithelial relic of the original pouch); in 13 others as an adenoma, 9 of these being designated as strumas; in 27 as a sarcoma (lymphosarcoma, 5 angiosarcomas, 1 perithelioma, and 8 endotheliomas); in 15 cases cysts were encountered; in others there were various lesions—3 gliomas, 2 teratomas, 7 tubercles, 3 gummas, 1 chondroma, 1 steatoma, etc. In addition, there were 15 cases in which the hypophysis was secondarily implicated; by osteosarcomas in 7, by meningeal endotheliomas in 4, and in 4 by glioma or sarcoma of the cerebral substance."

Cushing summarizes his pituitary tumor cases as follows, stating that in 29 cases he demonstrated certified lesions:

> "There have been 23 homoplastic epithelial growths or strumas originating from the gland itself. Of these, the struma in 2 cases of comparatively recent acromegaly was relatively small and showed an apparent hyperplasia of normal anterior lobe elements; while in a third,

a giant who was showing signs of ultimate glandular insufficiency, an obvious former anterior lobe enlargement had undergone a cystic degeneration. The 20 other cases all showed large strumas of chromophobe cells, with co-existent symptoms of hypopituitarism. With the one exception of a large hemorrhagic cyst, the tumors have been solid.

"There have been 6 heteroplastic or extra-pituitary tumors. Of those originating in all probability from a developmental rest, 2 were teratomas which had dislocated the gland and infundibulum forward and upward, and 2, infundibular cysts which had dislocated the same structures downward and backward. In addition, there has been one superimposed endothelioma, which possibly arose from the superior dural diaphragm.

"So far as the character of these growths concerns the much-mooted question of clinical hyperpituitarism *versus* clinical hypopituitarism, it can be said that no case of acromegaly has been associated with a heteroplastic tumor except one in which a glandular hyperplasia and a cerebellar cyst were co-existent; furthermore, that in all cases of acromegaly in which a large homoplastic chromophobe struma was demonstrated, evidences of glandular insufficiency had begun to be apparent.

"On the other hand, manifestations of primary hypopituitarism always accompanied the heteroplastic tumors which served to compress the gland, and were often an accompaniment, also of the large chromophobe strumas. These enlargements may occur, therefore, in glands that have not undergone the primary hyperplastic transformation to which acromegaly is commonly accredited."

Low blood-pressure was the only marked circulatory disturbance or sign. The respiratory tract was normal. The digestive tract was affected only as far as could be determined clinically by spasticity of the colon, helping to produce the abdominal pains and meteorism. The genito-urinary system was not particularly affected; the testicles were not decreased in size, although they may have been deficient in interstitial tissue. There was an early loss of libido, following the onset of the first symptoms of polyuria. Operative evidence and the clinical symptoms would indicate that there was a probability of pressure upon the peduncle of the cerebellum, causing the ataxia and disturbances of gait. There was undoubted marked pressure upon the chiasm, as the cause for the hemianopsia, which finally resulted in the complete optic atrophy. The osseous system was not decidedly affected. There was no arrest, retardation or elongation of the long bones. The acral bones, the short and the flat bones were not decidedly affected. This is additional proof that there probably was no secretory disturbance of the anterior lobe of this gland, except for a short time during the second three years of the course. Among the endocrine glands there was possibly some deficiency of the suprarenals, as a cause for the slight impregnation of pigment over the face and the rest of the skin. There is no clinical evidence of thymus involvement. The thyroid probably became deficient later in the course of the disease, producing the thickening of the subdermal tissue and the padding of the backs of the hands and the supraclavicular spaces. The parathyroid and the pineal give no clinical evidence of change. The blood showed an absence of eosinophils, which are usually reported as being present in these cases. There was a slight lymphocytosis. The skin was slightly rough, dry, and thickened in its subdermal structure, due, as stated above, to the late thyroid insufficiency. The organs of special sense were not affected except that of the eye, which has been described in detail in other sections.

SECTION 5

PITUITARY OBESITY

The following 2 cases are described as classical illustrations of *pituitary obesity* (Fröhlich's disease, dystrophy adiposogenitalis). The first case (VII) is a pre-adolescent case in a male, showing the typical hypoplasia of the genitalia, associated with the enormous obesity. The second (VIII) is a postadolescent case in the female, demonstrating the *enormous obesity, without* the decided *aplasia* of the genital tract, due to its occurrence after these organs had already been developed. The second case has as one of its most decided hormonic signs that of a very extensive chloasma pigmentation, which the authors contend is due to the secretory disturbance of the anterior lobe of the pituitary, and not to a secondary involvement of the adrenal. Both are classical bilobar insufficiencies of the hypophysis, the difference in the hormonic signs being due entirely to the different ages at which the inactivity of the gland occurred.

A. Bilobar Insufficiency of the Pre-adolescent, Aneoplastic Type

Etiology.—There is no definite acquired disease or trauma which might be related to the functional disturbance of the pituitary gland in this case (VII). The patient had measles, whooping-cough, and diphtheria as a child, but no definite illnesses between the ages of eight and ten. The past history is also free from injuries and operations. The family history, however, undoubtedly has definite bearing upon the secretory disease present in this case. Three previous generations on the maternal side had definite signs of obesity, which was probably of pituitary origin. An aunt of the patient is under personal observation for a typical bilobar pituitary insufficiency, and will be described as Case XV. One brother died suddenly during the second day of life—a possible case of lymphatism. The writers have found this familial line of ductless gland dyscrasias a very important diagnostic point. It has long been recognized by the laymen as the cause of hereditary traits and tendencies, but very little importance has been given to it by the clinician as a definite cause for inherited endocrinous dyscrasias. This heredity pertains not only to physical development, proportions, and resemblance, but also to emotional states, psychic disturbances, and mentality.

Symptomatology.—HISTORY: Case VII.—Master Wm. M., schoolboy, aged sixteen, examined at St. John's Hospital, October, 1917.

Present.—Chief Complaints: (1) *Vertiginous attacks,* sufficient to force the patient to sit down, although he has never fallen. The patient at times is forced to resort to support to retain the upright position. This is associated with some dyspnea and pain at about the second and third anterior interspaces of the left chest. (2) *General hyperesthesia* over the entire body both to deep and superficial palpation. (3) *Diminution in visual acuity,* some lacrimation and smarting. (4) *Diffuse headache,* early in the morning. (5) *Gastric disturbance,* particularly *nausea* and *vomiting,* periodical in type. Visual scotomata, but headache not particularly intensified at that time. (6) Marked *softness* and *early degeneration* of the teeth, tendency to crumbling. (7) Remarkable *gain* in *weight,* coming on suddenly at the age of ten years, and considerably increased since that time. The present weight is 195 pounds. The patient does not know just how much or how rapidly he has gained.

Duration.—Six years.

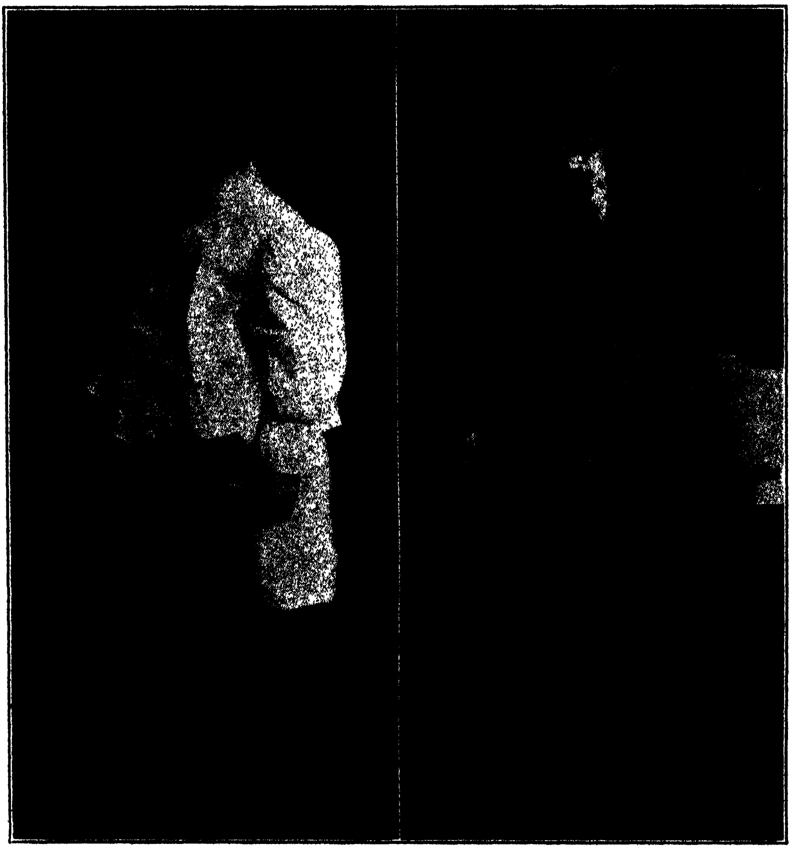
Course.—(*a*) *Onset:* sudden. The patient gives a history of having had *more or less trouble since birth.* Delivery was normal, the baby bottle-fed. Considerable *gastric disturbance was present in early infancy;* frequent tonsillitis and gastric disturbance until five or six years ago. At that time the patient, a normally formed and developed boy, had his tonsils and adenoids removed. Following this, the remarkable development and growth commenced. The patient *took on weight* rapidly, at the age of ten, with a tendency to the type to be described under General Examination—namely, *the girdle obesity.*

(*b*) *Progress.*—The obesity has been increasing consistently, until at the present time the patient weighs 195 pounds. He takes *considerable exercise and eats in moderation.* Despite the exercise and dieting, the patient still continues to have gastric disturbances and to gain in weight. Since the beginning of the adiposity, the patient has complained of *vertigo,* coming on at no particular time, frequently severe, requiring support, never producing falling or loss of consciousness. This is occasionally associated with pain high in the precordium, at about the second and third interspaces, with some dyspnea. The hyperesthesia, both to superficial and deep palpation, has developed. Headaches, particularly in the morning, diffuse in type, are intermittently present. Diminution in vision has occurred since the age of twelve. The *teeth* have always had a tendency to be *soft* and *"crumbling"* in character. The *baby teeth fell out almost as soon as dentition had taken place,* and the present teeth have undergone marked degeneration, which may be seen in the photograph. The fat padding, described under the general examination, occurs about the *neck,* posteriorly, the *mammary glands,* and more markedly in the *hypogastric region* and over the *mons.* The typical girdle obesity, extending down to the midportions of the thighs, is evident, the adiposity being less marked in the arms and the legs. The patient has not grown much in height since the age of twelve. The genitalia have remained undeveloped. No secondary sexual characters have appeared. There are no signs or symptoms referable to other systems.

Past.—Measles, whooping cough, diphtheria, frequent colds and sore throat, "bronchial trouble." No injuries or operations.

Personal.—Sleep occasionally disturbed, due to restlessness. Appetite good, but the patient is a moderate eater at the present time. Bowels regular. No history of polyuria or polyphagia.

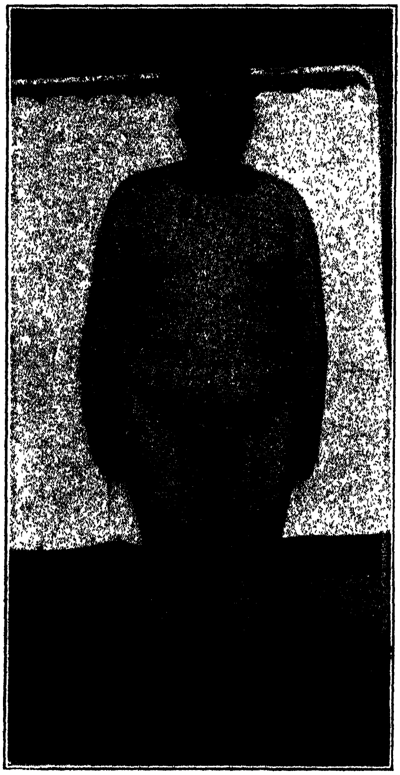
Family.—Father living, aged fifty-two, had asthma, but according to description, no definite hormonic signs, no tendency to girdle type of obesity, etc. Mother living, aged forty-five, large woman, tendency to girdle obesity and to large mammary development. One brother died suddenly on the night following birth, while at breast; diagnosis of heart condition. One brother died at the age of nine, possibly from pneumonia and heart trouble; always delicate. Patient's great-great-grandmother, great-grandmother, mother, and maternal aunt, tendency to be very large, of the girdle type of obesity, the chain being broken only in the case of the grandmother, who was of medium size. On paternal side, no particular tendency. Aunt is case of postadolescent bilobar hypopituitarism, to be described in this series as Case XV.



A B

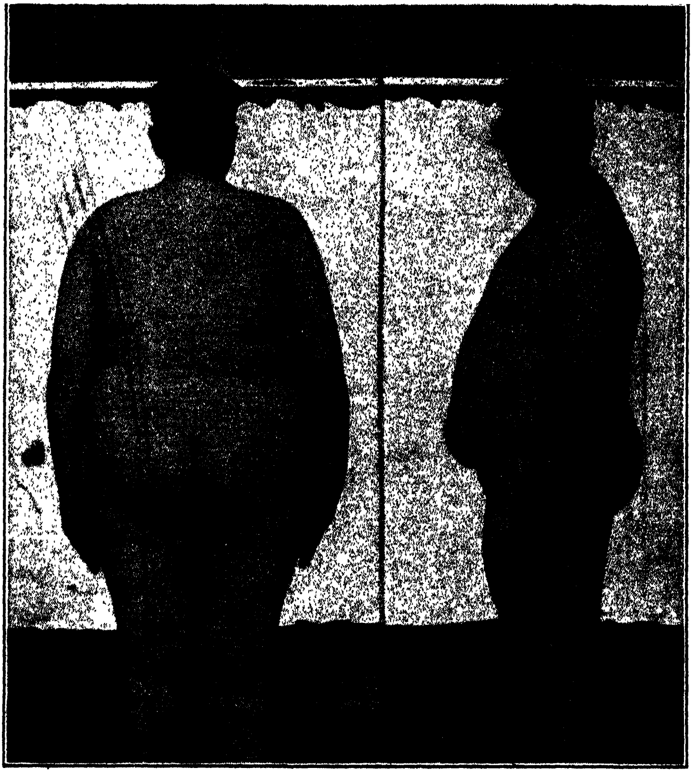
CASE VII. Fig. 1.—(a) Aged Six. (b) Aged Twelve. Note Beginning Obesity of Classical Type.

Examination.—*General.*—Very obese young man, with enormous girdle adiposity, marked hypogastric folds and padding. Long bones short, hands particularly small in comparison with remainder of body. Feet small, not so marked as hands, some cuffing about ankles. Hands and feet cold. No marked scars or pigmentations. Complete *absence of secondary sexual characters;* axillary and pubic hair absent. Hips markedly full, padding in lateral aspects and in axillæ. Very marked superficial hyperesthesia. Patient remarks that every time he is struck, the spot hurts for two or three days. Veins show through skin prominently. *Mammary development marked,* neck very short, marked fullness below clavicles. *Penis very small* (one inch), *testicles pea size.* Pulse slow, low volume and tension, equal, symmetrical. Measurements: Height, 5 feet 4 inches (163 cm.); from vertex to symphysis, 34 inches (86 cm.); from symphysis to soles of feet, 30 inches (76 cm.); circumference of head, 21½ inches (54 cm.); chest expansion, 42 inches (107 cm.); hips, 51 inches (130 cm.); arms, 51 inches (130 cm.); humerus, 10 inches (25 cm.); legs, 19 inches (48 cm.). Weight, 195 pounds.



CASE VII. FIG. 2.—AGED FIFTEEN, ANTERIOR VIEW. NOTE SMALL HEAD, HANDS, AND FEET, TYPICAL PITUITARY HEAD, CLASSICAL OBESITY, AND HYPOPLASIA OF GENITALIA.

Regional.—Head: Hair normal in texture, low on forehead. Lanugal growth meeting eyebrows in both supra-orbital regions, lanugo extending from lateral aspects of cheeks to angles of jaw. Head *rounded, small.* No localized compression tenderness over muscle attachments, sinuses, or nerve exits. Dilatation of superficial venules over the malar processes. No tendency to hexagonal shape of face. Occasional pigmented mole, no other pigmentations or skin lesions about the face. *Ears:* Air and bone conduction normal. Rinne's test positive. External ears well colored, no tophi. *Eyes:* Eyebrows somewhat thinned at outer margins, blending into lanugal growth which extends upward to the hairline. Lashes normal. Pupils equal, concentric, regular in contour, react promptly to light and to accommodation. Eye-muscles intact, no thyroid signs, palpebral slits rather narrow. Some fullness of the upper lids, scleræ and conjunctivæ negative. *Nose:* Bridge well formed, no marked blunting of the tip, septum straight. Mucous membranes normal. *Mouth:* Mucous membranes well colored, some dilata-

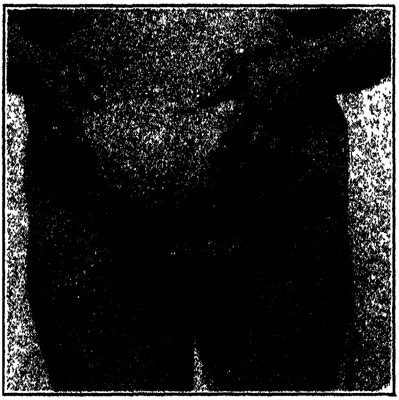


CASE VII. FIG. 3.—(A) POSTERIOR VIEW. NOTE BROAD PELVIS AND ENORMOUS GIRDLE OBESITY. (B) LATERAL VIEW. NOTE THORACIC, ABDOMINAL, AND MONS FAT PADS.

tion of superficial venules, no pigmentations. Tongue coated posteriorly. Teeth very *soft, upper central incisors* show very peculiar formation, *marked hollowing and indentation.* Lateral portions pointed. (*See* photograph.) Lower incisors show *marked serration and transverse ridging.* Remainder of teeth poorly developed, tendency to be soft. Tonsils absent, pharynx normal. *Neck:* Very short, thyroid not enlarged, veins and glands normal. *Chest:* Well covered, shoulders broad, well formed. Marked axillary padding, peculiar flaring of the hips. *Mammary development exaggerated, and from that region down to the mons, fat falls in successive ridges,* the upper folds being the mammary and limited to a line drawn beneath the bases. Succeeding fold not so marked; *fold below the umbilicus extending to the mons decidedly more marked* than the upper folds. Below this is another pad of fat, involving the mons and extending to the genitalia. There is marked padding in the posterior cervical region, particularly marked about the *seventh cervical vertebra.* Expansion fair, equal, tactile fremitus equal, symmetrical, percussion note of normal resonance throughout. No abnormal transmission of voice, breath, or whispered sounds, no râles, rubs, or other adventitious chest sounds. *Abdomen: Marked sensitiveness over the entire abdomen,* to both superficial and deep palpation. Abdomen very broad, girdle obesity type, with large folds of fat as described, particularly from the umbilicus down to the mons. This obesity extends over the hips, down to the midportions

VII. FIG. 4.—NOTE DEDENTITION.

of the thighs. No pain, tenderness, increased resistance, or rigidity of the abdomen; no tumefactions or dullness, including deep in the flanks. *Liver:* Dullness on normal borders, no liver dullness below the costal arch. Liver edge not palpable below the costal arch. Gall-bladder region free from tenderness, tumefaction, and dullness. *Spleen:* Not enlarged to palpation or percussion. *Kidneys:* Not palpable. *Colon:* Cecum and sigmoid not made out. *Genitalia: Testes decidedly small, pea size; penis one inch long, infantile size. Extremities: Long bones very short,* out of proportion to the remainder of the body. Hands small, with dorsal padding, particularly on the dorsal aspects of the first phalanges. *Fingers tapering,* nails small, not particularly atrophic. *Thighs very full down to the middle portions, where there is a marked dropping off in diameter.* Legs large and well formed. There is an ecchymotic discoloration over each thigh. *Feet small,* some padding about the ankles. *Reflexes:* Babinski, Chaddock, Gordon, Oppenheim, negative. Achilles, patellars, cremasterics, present. Abdominals, pectorals, forearm, biceps, triceps, radio-ulnar, present. Jaw-jerk present, Chvostek negative.



CASE VII. FIG. 5.—NOTE TAPERING FINGERS, ABDOMINAL AND MONS FAT PADS, AND TINY GENITALIA.

LABORATORY FINDINGS.—*Urine.*—Single specimen, color amber, reaction acid, specific gravity 1.020. Dextrose, albumin, leukocytes, erythrocytes, and casts negative.

Blood:

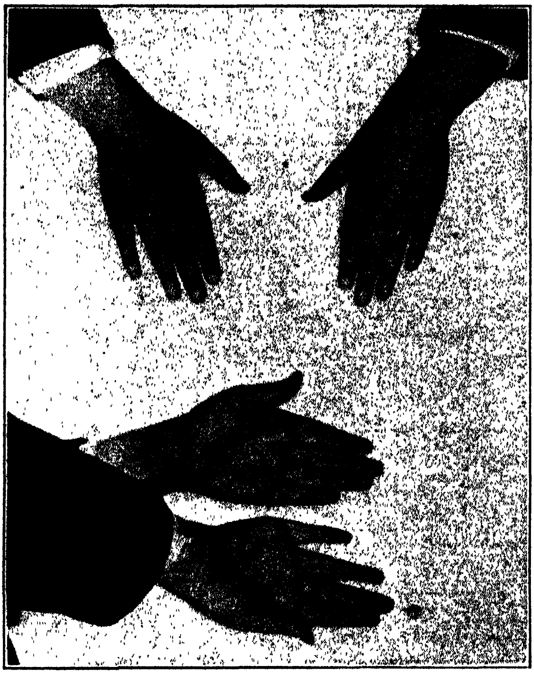
Erythrocytes	5,650,000
Leukocytes	6,200
Hemoglobin	102 per cent.
Wassermann	negative

Differential analysis:

Neutrophils	57 per cent.
Basophils	0 " "
Eosinophils	1 " "
Lymphocytes (large)	30 " "
Lymphocytes (small)	10 " "
Transitionals	2 " "

Chemical Blood:

Blood-sugar	0.074 per cent.



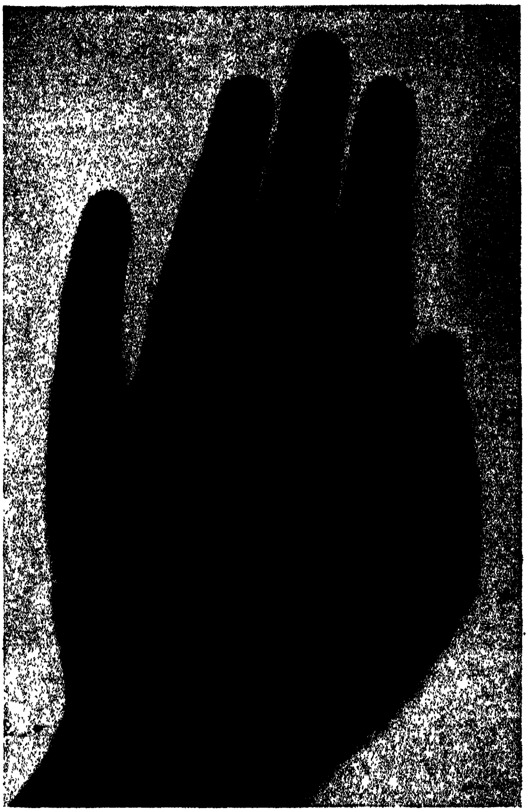
CASE VII. FIG. 6.—NOTE DETAIL OF CLASSICAL HANDS, NARROW DORSA, FREE FROM FAT PADS, TAPERING TERMINAL PHALANGES, AND SMALL NAILS.

SPECIAL EXAMINATIONS.—*Roentgenogram of Hand.*—Long, slender phalanges, absence of closure of the epiphyseal phalangeal heads. Absence of tuberosities or tufting of the terminal phalanges.

Roentgenogram of Head (Transverse View).—Small sella turcica, anterior-posterior diameter 12 mm., depth 10 mm. Frontal sinus small; other markings normal for age.

Perimeter Examination (Dr. E. P. North).—Perimeter chart normal.

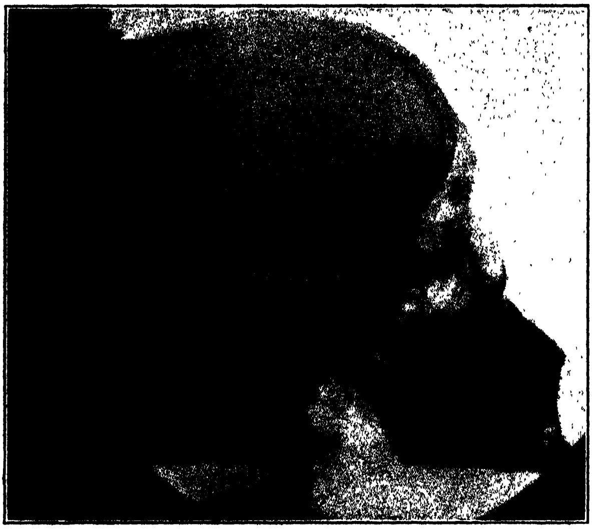
Diagnosis: *Hypopituitarism, Bilobar Involvement, Pre-adolescent Variety, without Pituitary Neoplasm.*—The basis for the diagnosis of hyposecretion of the two lobes in this case is as follows: (1) *Anterior lobe:* (*a*) arrested skeletal development, short long bones, small hands, head, and acral bones; (*b*) aplasia of the genitalia. (2) *Posterior lobe:* (*a*) history of sudden rapid gain in weight; (*b*) classical girdle and mons adiposity; (*c*) high sugar tolerance, slow pulse, subnormal temperature. (3) *Aneoplastic type:* (*a*) Small sella turcica; (*b*) absence of signs of pituitary neighborhood intracranial pressure.



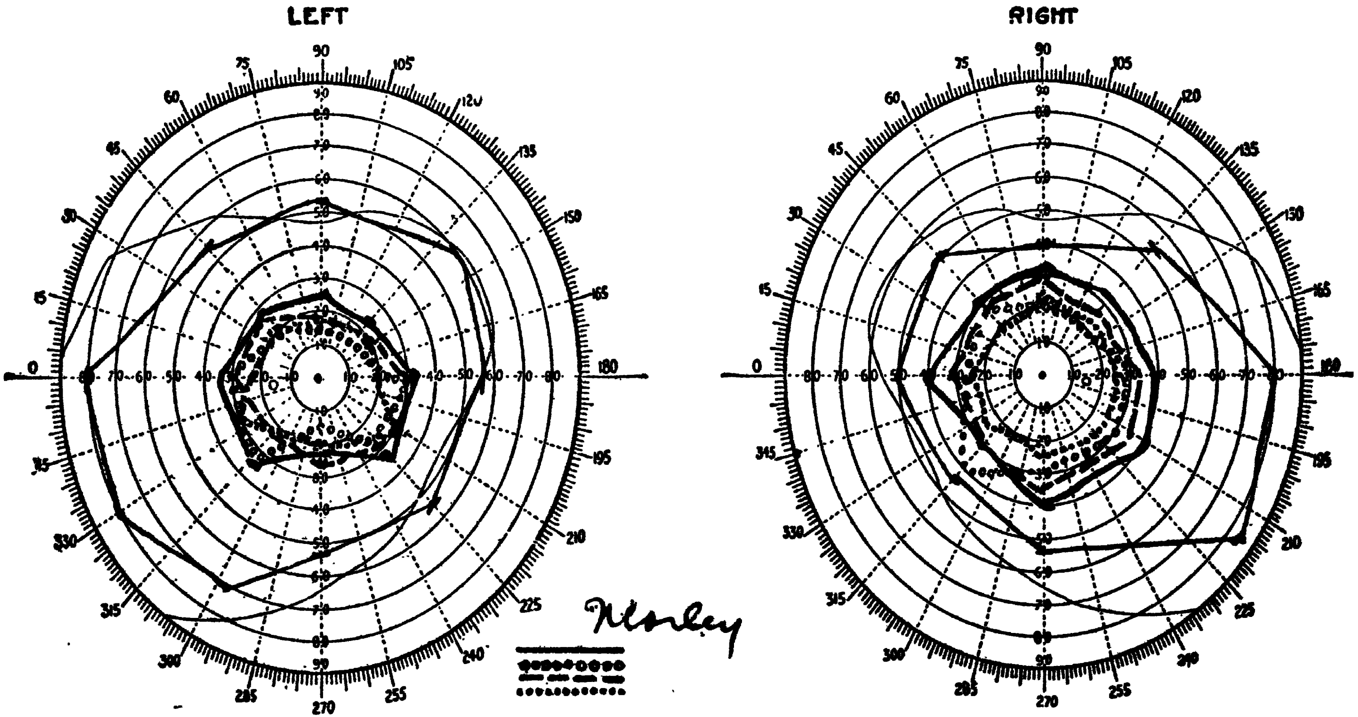
CASE VII. FIG. 7.—NOTE LONG, FRAGILE METACARPALS AND PHALANGES, AND TAPERING UNGUINAL PHALANGES, WITHOUT MUSHROOMING OR TUFTING.

The onset of this case, according to the clinical history, occurred at about the age of ten, when the patient suddenly began to gain weight and rapidly assume unusual proportions about the hips. There was no concomitant arrested growth occurring with the advent of this obesity. The patient's skeletal growth did not cease entirely, but there was no gradual increase in height following the age of twelve compared with the growth previous to that time. The aplasia of the genital tract was exceedingly marked and would compare with that of the average boy of four or five years, the penis being not longer than one inch and the testicles the size of small peas. This might indicate that there was a hypofunction of the anterior lobe much earlier than the age of ten, when obesity was first noticed. The hormonic effect upon the genitalia is probably of more significance with regard to the measure of the anterior lobe insufficiency, than the undergrowth of the osseous system.

Secondary sexual characters have not appeared at the age of sixteen. The feminine disposition of this boy has been noted since he has been under observation for treatment. He is inclined to associate almost entirely with females older than himself, and his habits are those ordinarily taken up by the opposite sex, such as cooking, sewing, household work, etc. The broad hips and genu valgum add to the feminine stature. The adiposity, while classically located, is not limited to the region of the body which a primary or essential pituitary disease would select. The localized obesity characteristic of pituitary disease is that of the girdle region—*from the navel down to the junction of the lower and the middle thirds of the thigh,* and *increased fat deposition in the mammæ and the mons.* There is an *absence of fat over the upper arm and the lower leg,* with *absence of fullness or padding of the dorsum of the hand.* This additional deposition of adipose tissue in this case would lead one to suspect a secondary involvement of the thyroid—slight hypothyroidism—as a complication resulting from the insufficiency of the pituitary gland. The skin, too, is somewhat thickened, inelastic, dry, and rough, which would be another evidence of a secondary hypofunction of the thyroid. The cause of this obesity has been attributed to the insufficiency of the posterior lobe of the hypophysis. Experiments carried out by Cushing, Goetsch, and Jacobson (Aschner) on



CASE VII. FIG. 8.—ROENTGENOGRAM OF SKULL.



CASE VII. Fig. 9.—Note Perimeter Chart Normal.

hypophysectomized animals, demonstrate conclusively that the posterior lobe insufficiency is accountable for the obesity, through its control of the metabolism. Hypersecretion of the posterior lobe is held by some accountable for the sexual infantilism. This may help to explain those peculiar non-obese cases having an overgrowth of the long bones very similar to that occurring in eunuchoids. If the excessive secretion of the posterior lobe is sufficient to depress or inactivate the interstitial tissue of the gonads, there would then occur a prolonged activity of the ossifying centers of the epiphyseal ends of the bones, particularly if the anterior lobe of the pituitary body was active, with the consequent overdevelopment of the long bones. Prolonged injections of posterior lobe substance in animals produces a decreased function of the gonads, associated with marked emaciation, overgrowth of the long bones, and finally death by cachexia.

The retarded skeletal development in this case is most instructive and significant. The almost completely arrested growth of the flat bones and the acral (peaked) bones, is absolutely consistent with an insufficiency of the anterior lobe of the pituitary gland. This is shown in the extremely small, rounded, yet classically shaped head; the small, pointed, well-proportioned nose; the triangular, narrow, sharp chin. The hands in this case are especially important to study. They are extremely narrow (narrowness shows underdevelopment of the carpal bones). The fingers and thumbs are not short or pudgy, compared with the remainder of the hand; in fact, they have a tendency to be long and pointed, which is particularly noticeable in the thumb and the little finger. The roentgenogram demonstrates an extremely long, slender phalangeal bone, *with absence of tufting or overgrowth of the tuberosity projections.* The writers wish to emphasize the fact of these bony markings because they are exactly opposite to what occurs in the hypersecretions of the anterior lobe, as in acromegaly (postadolescent hyperpituitarism). Much has been written regarding the overgrowth of these bones in acromegaly, but there is comparatively little said in the literature of *their underdevelopment,* a decidedly pathognomonic sign of the hyposecretions of the anterior lobe of the pituitary gland in the pre-adolescent individual. There are incomplete types of pre-adolescent hypopituitarism in which it is just these parts—the small head, hands, and feet—which demonstrate that the insufficiency of the anterior lobe occurred before maturity. There are cases in which these *acral* and *long* bones remain *undeveloped,* and later the anterior lobe *becomes hyperactive,* producing overdevelopment of these acral bones, without affecting the *long* bones, and resulting in the *short,* stocky acromegalic. In other cases occurring in pre-adolescence, the head, hands, and feet remain small during the entire life of the individual and may be the only evidence that there was a partial insufficiency of the anterior lobe of the pituitary gland during the early life of the individual. *These same bones undergo,* for a number of years, a *decided overgrowth* during the hyperactive state of the anterior lobe of the gland. Later, this lobe becomes *inactive* and *deficient in function* and frequently *changes into complete hypopitui-*

tarism, yet the head, nose, chin, lips, hands, and feet retain their overgrowth and characteristic type (of hyperfunction of the anterior lobe), as seen in the acromegalic. It is true that comparatively few of the bilobar group of both the anterior and the posterior lobe involvements of *hypopituitarism* ever change into the opposite form of *hyperpituitarism.* This does occur, however, in the unilobar variety involving only one lobe of the hypophysis, and is one of the causes for so much confusion and uncertainty regarding the identification and diagnosis of these diseases. In the unilobar hypopituitarisms, the course frequently is one in which *one lobe* has an inactive secretion for a time, such as primary *pre-adolescent* anterior lobe insufficiency, producing small hands, head, acral bones, etc., and, when later the posterior lobe becomes insufficient, producing the *typical postadolescent bilobar* hypopituitarism.

In our case, the anterior lobe was deficient during the early preadolescent age, as evidenced by the extremely small hands, head, etc., yet the absence of adiposity at that time demonstrated that the posterior lobe must have been *sufficient* at that age. The adiposity in cases occurring later in life (postadolescent) with a more decided previous reduction in the secretion of the anterior lobe, causing in the female a complete amenorrhea, goes to make up the finished, complete variety of postadolescent bilobar insufficiency of the hypophysis, characterized by the small hands, feet, and aplastic genitalia, with the *late addition* of the marked adiposity.

The high sugar tolerance in this case, as evidenced by the absence of an increase in the blood-sugar or of dextrose in a twenty-four-hour specimen of urine after the ingestion of 400 grams (14 ounces) of glucose, is indicative of posterior lobe insufficiency. This test has been given by investigators for years and accepted as a reliable measure for carbohydrate tolerance. It is well known, however, that this is not specific for pituitary disease, since hypofunctions of other glands, particularly of the thyroid and the adrenals, have this same high tolerance for carbohydrates. Recently, Janney, and Isaacson, as well as Allen, Hulston, and Taylor, have questioned the certainty or value of this method of estimating the carbohydrate tolerance. They call attention to the fact that there is no actual upper limit to sugar tolerance, so far as the normal individual is concerned. They are able to tolerate as much glucose as they can retain. Therefore, they argue that increased tolerance must be non-existent, and their observations have cast some doubt upon the whole conception of increased sugar tolerance. From the results of physiological experiments, they determined that a pure glucose solution, of a certain concentration per kilogram of body weight, would be absorbed even by different persons at a fairly uniform rate; it was, therefore, obviously necessary to study the rate of the alimentary absorption of sugar. Blood-sugar estimation enabled them to do this, it being known that blood-sugar was elevated when carbohydrates were ingested. It was found that following glucose ingestion, *normal* individuals uniformly reacted with a definite degree of hyperglycemia.

By measuring the blood-sugar *at short intervals,* it was possible to make out the normal blood-sugar curve. This was found to be so constant by them, as well as by Jacobson, Blohm, Hopkins, and Cummings, that they felt that it could be used as a measure of carbohydrate tolerance. Individuals not having this classical normal blood-sugar curve, made at short intervals following the ingestion of glucose, in this given concentration per kilogram of body weight, could definitely be considered either as having increased or decreased their carbohydrate tolerance. Wilder and Sansum, Sansum and Woodyatt, worked out what is probably the most accurate method yet described for testing the urinary glucose tolerance. They used intravenous injections of glucose, carefully controlling the rate of the supply of the glucose to the body by a special apparatus. They give as normal an intravenous injection of 0.8 gram of glucose, per kilogram of body weight, per hour. When more sugar is injected, glucose appears in the urine. The serious objection to this method is its difficult technic, which will probably prevent its adoption for ordinary clinical purposes. Contrary to the investigations made by these recent investigators, it is probable that an absence of marked increase in the blood-sugar or presence of glucose in the twenty-four-hour specimen of urine, following the ingestion of a large amount of glucose (400 to 500 grams) (14 to 18 ounces) undoubtedly can be accepted as confirmatory evidence of the decreased metabolism which is present in the insufficiency of the posterior lobe of the pituitary gland in hypofunctionating diseases of the hypophysis. In many personal observations, it was frequently noted that in underactivity of the *anterior lobe* the quantity of blood-sugar was lower following the ingestion of this large amount of glucose than it was at the examination made previous to the carbohydrate test, when only a comparatively small amount of carbohydrates had been taken. It should be borne in mind that adrenalin injections are given during the ingestion of these carbohydrates for the purpose of further stimulating the immobilization of the glycogen. The value of the pilocarpin and the atropin tests for posterior lobe insufficiency, is also questionable. The production of an increase of temperature, by giving these individuals an injection of minims xxx (2 c.c.) of a 5 per cent. solution of extract of the anterior lobe of the pituitary body, as recommended by Cushing, is also of uncertain value. In the authors' case, for instance, there was no rise of temperature following these injections, and they have had very few cases among their bilobar series confirming the efficacy of this test. Other authorities (Falta and Meyers) have not been able to place much value upon or to confirm Cushing's expectations regarding the diagnostic importance of this thermic test as a measure of the insufficiency of the *anterior lobe* of the hypophysis.

The absence of pituitary tumor in this case is based upon the negative evidence of enlargement of the sella turcica, as demonstrated by the roentgenogram, and upon the negative clinical evidence of pressure symptoms in this neighborhood, the normal perimeter reading, the absence of paralysis of the cranial nerve or effect of pressure upon other neighborhood tissue, and the lack of general intracranial pressure syndrome, such as nausea, vomiting, headache, and hydrocephalic signs. The sella turcica in this case, in fact, was *very much smaller* than in the normal individual of the same age, but compares fairly well with the size of the head. This *small sella turcica* had been a rather constant sign in the pre-adolescent type of hypopituitarism not associated with pituitary tumor, and the writers consider it *as significant as a large sella turcica indicating the presence of a pituitary tumor.* For instance, in those cases of hypopituitarism occurring after the age of maturity, the *small sella turcica is not such a constant sign* as in the cases occurring *before* the age of adolescence.

The degree of insufficiency in this case is interesting to consider and important to measure, for the reason that it probably has very decided prognostic value. It is more than probable that the totally complete insufficiencies of this gland, involving both the anterior and the posterior lobes, are more unfavorable with regard to relief of the deformities and deficiencies, such as impotence, sterility, lack of sexuality, etc., than a case that has only a partial or incomplete insufficiency of a single lobe of this gland. The same holds true with regard to prognosis concerning the duration of the disease. It is more than likely that a pure anterior lobe insufficiency is very much more favorable, as to duration of life and severity of symptoms, than one in which there is, in addition, a decided posterior lobe involvement. It is not at all probable that medical treatment applied in the form of organotherapy would be very effective if the functions of both lobes of this gland were decidedly decreased. There must be some function retained by the anterior lobe of this gland, since life would be incompatible without some function of this lobe, as has been proved by experiments on animals and operations on human cases. That the deficiency is quite marked in this case, however, is evident from the complete absence of growth of the genital tract and the almost complete arrest of the skeletal growth. The degree of the deficiency of the posterior lobe is also decided, as is evidenced by the enormous obesity. The fact that there has been absolutely no reaction to the ordinary dose injections, both of anterior and posterior lobe substances of this gland, proves that its function must be decidedly low.

Complications.—During the six months' observation of this case, there have been no decided complications referable to the other systems of the body. There is undoubtedly a disturbance of the function of the other ductless glands. The tendency to universal adiposity and to changes in the skin is clinical evidence of decreased secretion of the thyroid. If thyroid therapy should relieve to a certain extent the general obesity and change the texture and character of the skin, this will be additional proof that there is secondary thyroid insufficiency. That the hypophysis, and not the thyroid, is primarily involved, is unquestionable. The *absence* of supraclavicular fat pads, the tendency to padding of the backs of the hands, the decreased retardation of the ossifying centers of the carpal bones, the character of the head, the absence of a retroussé type of nose, etc., all prove conclusively that the thyroid, if it is involved, is only affected secondarily. There is no clinical evidence of an enlarged thymus. Absence of anterior mediastinal pressure symptoms, such as engorgement of the head, neck, and arms, from pressure of the superior vena cava; substernal fullness and pressure; systolic murmur over the pulmonic area, due to pressure on the right pulmonary artery; or evidence of pressure on any other structure in the anterior mediastinum, as paralysis of the left vocal cord due to pressure on the left recurrent nerve, is negative evidence in this case. There is no clinical proof of disturbances of the adrenal functions, as shown by chloasma, diffuse pigmentations, disturbance of blood-pressure, marked vasomotor pressure abnormalities, or abnormal distribution of hair. The clinical evidence of involvement of the pineal and the parathyroid glands is also negative.

Associated Diseases.—There is no definite association of this condition with the previous dyscrasia of the pituitary gland, as is frequently the case in an exceedingly large number of postadolescent hypofunctions of the pituitary gland, in which there had been, previous to the decreased functions of this gland, a hypersecretion of the hypophysis. This is evidenced in the majority of cases occurring later in life, by the antecedent history of polyuria, polydipsia, etc., indicating increased secretions of the posterior lobe, as well as by the physical changes in the long, short, or flat bones, the genital tract, or the deposition of fat. This case must be a primary insufficiency which has not been preceded by an overactivity of the pituitary. It is important to take this fact into consideration for the purpose of prognosis. These primary insufficiencies, provided they are not too decided or progressive in character, certainly should afford a better prognosis than the latter insufficiencies which are secondary or sequential to hyperfunctions of the gland. This type is also very much more likely to be only an intermittent condition, that is, existing only for a certain number of years, and to be less complete and not progressive, than other hyposecretions of the pituitary which have followed hypersecretions of this gland. All these facts, of course, make the prognosis more hopeful and favorable, both as to positive relief of the symptoms and as to the duration of life. The family history is extremely instructive in that it portrays ductless gland disease in a number of other members. The mother was probably a hypophysopath. One brother died very suddenly in childhood, possibly a thymic death. The history of obesity recurs in a large percentage of the family for three generations. The patient's aunt is under observation at the present time and will be described in the following series of postadolescent hypopituitarism. She is a bilobar variety, having all the classical markings of deficiency of the pituitary gland, which came on at the age of seventeen. Considering the more than common relationship of the deficiencies of the pituitary gland to lues, one would suspect the possibility of hereditary lues in this family, although the serological reactions for this disease both in the patient and his aunt have been negative.

Clinical Varieties.—This case is classified as a pre-adolescent, bilobar, aneoplastic hypopituitarism, according to the grouping of these diseases as made under the heading of Introduction, at the beginning of this article. Reference to this classification will show that both the hypo- and the hyperpituitarisms were divided into (*A*) those cases in which the anterior lobe is independently involved, (*B*) those in which the posterior lobe is affected, without disturbance of the anterior lobe, and (*C*) those in which the entire gland (both lobes) is implicated in abnormal function and secretion. Each one of the unilobar and the bilobar subdivisions was subdivided into (1) the pre- and (2) the post-adolescent varieties. These varieties were again subdivided into (*a*) those cases associated with neoplastic changes in the pituitary, and (*b*) those without evidence of pituitary tumor.

The history of the onset of the adiposity at the age of ten; the arrest of the skeletal growth at the age of twelve; the absence of development of the genitalia and secondary sexual characteristics, classify this case as the pre-adolescent variety. The absence of the enlargement of the sella turcica, and the negative signs and symptoms of intracranial pressure in the neighborhood of the pituitary body, prove that it is of the aneoplastic type. The grouping of this case with the hypopituitarisms depends entirely upon the correct interpretation of the hormonic signs both of the anterior and the posterior lobes of the hypophysis. There are no regional or focalized evidences about the pituitary gland itself which would identify this gland as the cause of the marked deformities and disproportions of the body, the undergrowth and absence of function of the gonads.

Previous analysis of the hormonic signs of the case herewith reported (Case VII) demonstrates that both lobes are decidedly affected. This classification assumes the premise that there is sufficient knowledge extant to identify the hormonic changes in the body as a whole or in its individual organ functions, as specific of each individual lobe of this gland. It is necessary first then to separate distinctly those hormonic signs present in distant structures produced by the change in function of the anterior lobe, from those due to change in function or secretion of the posterior lobe. In Section 4 (Case V) the hormonic signs pertaining both to the hypo- and the hypersecretions of the *posterior lobe* were reassembled and analyzed. By referring to this section, it will be noted that the functions of this lobe affected the following structures and functions—metabolism, blood-pressure, temperature, pulse-rate, disturbances of the nervous system, involuntary muscle contractions, dermal system, endocrine and other secretions.

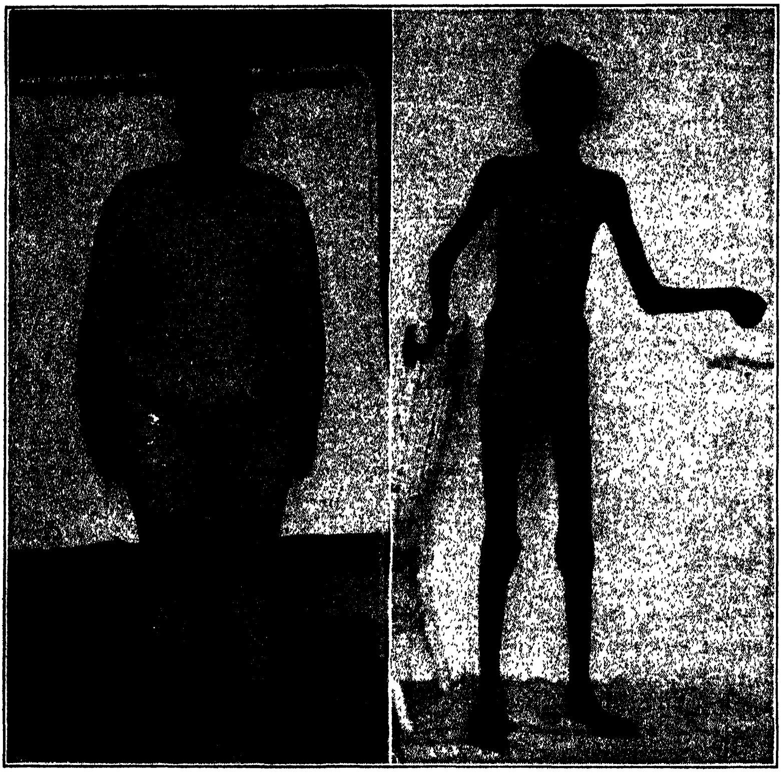
In consulting the table on the hormonic signs or effects of the function of the posterior lobe on other systems of the body, it will be seen that the *hypofunction* of this lobe is *exactly opposite* to the *hyperfunction,* with the slight exception of difference due to the age (pre- or postadolescent) at which the abnormal activity of the lobe occurred. In comparing the hormonic signs of the posterior lobe with those of the anterior lobe, the most significant fact to bear in mind is that these two lobes of the hypophysis have very decidedly different functional actions, not only acting upon entirely different tissues, but also apparently with entirely different purposes. The posterior lobe has to do, to a large extent, directly with the metabolism or indirectly with other functions and secretions which play an important part in metabolic changes in the body. For instance, the secretion of this lobe controls the carbohydrate metabolism and sugar tolerance, and is probably definitely related to the other internal secretions such as the adrenal, the thyroid, and probably the pancreatic, which almost entirely control and regulate the metabolic changes of the body. Its effect upon the blood-pressure, the involuntary muscle contractions, the temperature, and the pulse-rate, are also related indirectly to the action of either anabolic or catabolic bodily changes. The disturbances noted in the disease of this lobe of the gland, in the nervous system, the dermal system, the secretions of the skin, the gastro-intestinal and the genito-urinary systems, can all be connected more or less definitely with the ordinary catabolic changes of the normal individual.

In contrast with *these functions of the posterior lobe* are those of the anterior lobe, which *deal to a large extent* with changes in *growth* and *development* of the two primarily affected systems—the *osseous* and the *genital.* These systems are *not affected* either by a hyper- or a hyposecretion of the posterior lobe. In order to impress the significance of the independent function of the anterior lobe, reassembling and analysis of its hormonic signs have been thought necessary. To make the interpretation of these hormonic signs less difficult and confusing, those pertaining to an underactivity of this lobe have been contrasted with those produced by an overactivity of the functions or secretions of this lobe of the hypophysis. In comparing the analysis made of the hormonic signs of the anterior with those of the posterior lobe of the hypophysis, it will be seen that the dermal system and the temperature have been classified as signs referable to both lobes. This is due to the fact that there is still some question with regard to the changes present in this system or function, *i. e.*, as to whether they are produced by the anterior or the posterior lobe. Cushing has always been inclined to believe that the subnormal temperature, for instance, is due to inactivity of the anterior lobe. He attempted to prove that injections of extracts of this lobe would restore the temperature in these activities to normal, and used this as a test for anterior lobe insufficiency. The changes in the dermal system present in independent disturbances of each lobe, both anterior and posterior, are probably best explained by the associated changes in other glands such as the thyroid and the adrenals, which are sooner or later involved in diseases of the lobes of the hypophysis. As a matter of fact, there are also changes in the osseous system which some have attributed to disturbance of function of the posterior lobe. It is known, for instance, that in insufficiency or inactivity of the gonads, present in eunuchs, there is late closure of the epiphyseal centers of ossification. This produces the unusual overgrowth of the long bones in these individuals. Hypersecretion of the posterior lobe of the pituitary is given credit by some for producing insufficiency of the interstitial substances of these gonads. In this indirect way it can be seen how the posterior lobe of the pituitary might affect skeletal growth. The second case reported in Section 4 (Case VI) helped to disprove this assertion. In the authors' case, which was undoubtedly a pure dyscrasia of the posterior lobe, there was a very definite hyperactivity, during the first three years, followed by a six-year course of hypoactivity, and there was no evidence of decreased function or growth of the genitalia. This was also shown in Case V, in which a pre-adolescent posterior insufficiency was described, having an unusually well-developed genital system. This case gave a very definite history of hypersecretion of the posterior lobe, without an anterior lobe involvement, during the early course of the disease. There are other systems and organs necessarily affected by the function of each of these lobes, which produce an apparent overlapping of their hormonic effects; yet on the most scrutinizing analysis, these can usually be explained by the interaction of other ductless glandular secretions.

A perusal of the hormonic signs attributed to the individual lobes of this gland will also demonstrate the fact that the writers have attempted to account for these structural changes and functions in other portions of the body merely on the basis either of a decreased or an increased secretion from the individual lobes. It has not been thought necessary to attribute to these glands the further qualification of forming a secretion which is so different in character from the normal as to produce an entirely new and perverted effect upon other structures or functions. If this simple basis of explanation can be accepted, it will go far to dispel the vast group of disturbances which are now classified as dyspituitarisms, merely because they cannot be properly grouped with the now established hyperpituitarisms or hypopituitarisms.

In reviewing the diseases of the posterior lobe of the pituitary gland, one cannot but agree with the statement that those due to this lobe alone, either to hyper- or hyposecretion, have surely been poorly differentiated and separated. This has been due to a remarkable lack of knowledge regarding the physiological functions of the lobe, as well as of the entire gland. In those cases in the literature which are due to diseases of the anterior lobe, one is struck with the fact that the hypersecretions of this lobe are much better understood and described than the hyposecretions or deficiencies of function of the anterior lobe. In fact, the hypersecretions of the anterior lobe have been so well and frequently described that, until Froehlich's description of dystrophy adiposogenitalis, the diagnosis of pituitary disease was rarely made without definite findings either of local changes in the pituitary gland itself, or marked skeletal overgrowth due to hyperactivity of what was then supposed to be both lobes of the gland. After Froehlich's description in 1901, the knowledge of hypo- or inactivity of this gland received considerably more attention. Following this time, the addition of obesity and the absence of acromegalia as hormonic signs of insufficiency of the gland, have been the clinical picture sought as cardinal evidence for hypopituitarism. Few would venture to make such a diagnosis (of hypopituitarism) without either definite neighborhood pituitary signs, or obesity and the classical overgrowth of either the peaked or the long bones of hyperpituitarism.

A comparison of the pre-adolescent variety of hypopituitarism in which both lobes are involved (Case VII), with that of a posterior lobe insufficiency (Case V) demonstrates the striking clinical difference in the hormonic signs in these two conditions. In both these individuals (Cases V and VII) there is an insufficiency of the posterior lobe. In Case VII there was an insufficiency of this lobe, which had been continuous up to the time of the report. In Case V there was at the time of observation an undoubted *hyposecretion of the posterior lobe, which had been preceded by a hypersecretion* of this lobe. It is noticed that in Case VII the typical obesity, so graphically described by Froehlich, is present, while in Case V this obesity has been *entirely absent* during the entire course of the disease. Absence of this obesity has been re-



CASE VII. FIG. 10.—COMPARISON OF CASE VII, PRE-ADOLESCENT BILOBAR HYPOPITUITARISM (Left), WITH CASE V, PRE-ADOLESCENT POSTERIOR LOBE INSUFFICIENCY (Right).

ferred to in the report of Case VI, which at the time of observation was also a hyposecretion of the posterior lobe. These cases, as well as others personally observed or described in the literature, help to prove that those secondary posterior lobe insufficiencies (having precedent clinical history and signs of *hypersecretion* of the posterior lobe) *do not have the classical adiposity* which is present in those cases which are primary insufficiencies of the posterior lobe. Another interesting fact demonstrated by the comparison of these two cases is the sign of anterior lobe insufficiency in Case VII, which is absent in Case V. This is demonstrated by the arrested skeletal growth in Case VII (height, 5 feet 4 inches, at the age of sixteen), as compared with Case V (height, 5 feet 5 inches, at the age of fourteen). The difference in the genitalia is very striking, showing absolute undevelopment in Case VII (at sixteen), with unusual development in Case V (at fourteen). The broad hips and the genu valgum of Case VII contrast very strikingly with the narrow pelvis and widely separated knees in Case V. The marked difference in the size of the head, hands, and feet as compared with the length of the body, is also opposite in the two cases. In Case VII these bony parts are proportionately small, and in Case V they are unusually large as compared with the rest of the body. The tendency to eunuchoidism, the unusual distance between the symphysis and the soles of the feet, in Case V, as compared with the shortness of the same distance in Case VII, is quite noticeable.

Treatment.—PROPHYLACTIC.—The prophylactic treatment in these cases of hypopituitarism which are *not secondary to hyperpituitarism* and *not associated with pituitary tumor,* needs little consideration. In those cases which are secondary to other diseases, of course, the primary disease is the prime indication for treatment. In those cases of hypopituitarism which are secondary to *hyperpituitarism with a pituitary tumor,* **early surgical treatment** should be given the first thought. Many cases would probably be prevented from producing severe regional lesions, such as blindness due to chiasm pressure and other conditions due to general intracranial pressure, as well as from drifting into the terminal state of hypopituitarism, if the growing tumefaction of the pituitary gland was removed by operation.

ACTIVE TREATMENT.—In the primary hypopituitarism, *without tumor* of the pituitary gland or *other evidences of regional pressure effects* upon the chiasm, the uncinate gyrus, or other structures in relation to the pituitary gland, surgical intervention can be postponed until at least other treatment has been given reasonable trial. In some of these cases without tumor, however, there is some evidence of pressure upon the regional tissue in the neighborhood of the pituitary gland, such as epileptiform attacks, supposedly due to pressure upon the uncinate gyrus, in which surgical treatment should be considered. Cushing advised and did a **trans-sphenoidal decompression operation** upon the pituitary gland in these cases, even when there was no evidence of enlargement of this gland, manifested by a skiagraph of the sella turcica or by pressure upon the cranial nerves, etc. This was done with the point in view of possibly relieving some of the pressure of the bony socket containing the pituitary gland, which might have something to do with the causation of its inactivity. In the hands of an experienced operator, this rational treatment might even be considered as the initial procedure. Unless this skill and experience, however, is definitely at hand, probably a more conservative line of treatment in this type of case, in which the symptoms are not urgent and the evidence of progression not evident, is better practice. While it is true that **organotherapy** must admittedly be given without too much encouragement, its exhibition in these cases is unquestionably indicated. Glandular treatment should consist of desiccated substance of **both the anterior and the posterior lobes,** by mouth, given in large doses, combined with extracts of these lobes given intramuscularly. The estimation of the size of the dose in these cases has not been definitely determined. In fact, up to the present time, there is absolutely no standardization of either the desiccated gland or the extracts. The dosage will necessarily vary in the individual case, depending upon the type (uni- or bilobar) and the degree of inactivity of the lobes. Better results are to be expected in those insufficiencies which are limited to one or the other lobe or in the milder inactivities of the entire gland. Cushing attempted to measure the proper dosage by its effect upon the sugar tolerance; that is, he gave a sufficient amount of the desiccated gland to restore the sugar tolerance to normal. Even in some of the cases in which this was carried out, ideal results overcoming or controlling symptoms or signs were not accomplished. The extracts of both these lobes are obtainable on the market. **Pituitrin,** which is an extract of the posterior lobe and the infundibulum, has been used for a considerable length of time for other purposes, in obstetrical and surgical practice. This has been given intramuscularly, 0.5 to 2 c.c. (8 to 30 minims) at a dose, with intervals of from one to seven days between injections. Recently an attempt was made to measure the dose of the posterior lobe extract by its general reaction or its effect upon the intestinal peristalsis. In many cases of posterior lobe insufficiency, a reaction was observed a few minutes after intramuscular injection, consisting of severe abdominal cramps, soon followed by bowel movement, termed the "intestinal reaction." The dose is decreased below the point which produces this reaction. This dose is then continued daily or until the desired effect upon the obesity and other symptoms is obtained. The "general" reaction consists of tremor, general weakness, emotionalism, blanching of the skin, nausea, and sometimes vomiting. These signs are also taken as evidence of too large a dosage, and should be reduced to one which will not cause these general signs of pituitary intoxication. On account of its quick absorption, it is best given subcutaneously, by which administration its reaction is least marked. In the great majority of those insufficiencies which are decided enough to produce marked clinical manifestations, this dose (0.5 c.c. every seven days) may be too small and the interval too long. Some of the cases observed by the authors have not reacted favorably to the above treatment, and future observations will be directed toward giving much larger doses, at shorter intervals, measured by the effects of "general" and "intestinal" reactions. Besides the use of pituitary extracts in these cases, personal observation has demonstrated that there are *secondary disturbances in other ductless glands which require glandular treatment,* in the great majority of these cases which have existed for any length of time, or even in early cases which are sufficiently advanced to make the diagnosis fairly certain. In the discussion of hypopituitarism of the postadolescent group, definite cases will be described which will tend to prove the inefficacy of simple pituitary therapy, as compared with a **polyglandular therapy** directed toward the thyroid, the adrenals, and *the pituitary gland.* That is, pituitary extract alone failed to produce any change in symptoms in these cases,[4] while pituitary, thyroid, and ovarian extracts, and adrenalin, produced very marked amelioration of all constitutional symptoms, such as headache, fainting spells, thoracic pressure symptoms, abdominal ballooning, and amenorrhea. In one case particularly, the periods, which had been almost completely absent, or occurring only every six or eight months, were restored to normal amount and regularity for the past year. Concomitant with that, there was almost complete relief from the many varied symptoms ranging in location from the head to the pelvis. As to whether an early institution of this treatment in the pre-adolescent age would be as effective as it is in some of the postadolescent cases, lack of experience with this primary type at an early age will not permit a prophecy. One would suspect, however, that if the diagnosis is made in these cases before there are decided changes in the distal portions of the body, much more could be accomplished from the simple **substitution treatment.** In this case, it will be seen from the records that prolonged treatment over a course of six months, first of single injections of **anterior lobe extract,** then of **anterior pituitary lobe combined with desiccated thyroid,** has so far had no appreciable effect upon any of the signs, such as weight, aplasia of the genitalia, etc. It is true that the pituitary substance in this case has been given only in comparatively small doses, every seven days. After other combinations are attempted in this case, such as the addition of **posterior lobe extract** and **gonad substance,** larger doses of the combination of these substances will be given. From our personal observation and treatment of other cases, this is the only means we have at the present time of deciding definitely either the dosage or the glandular substance to be combined. As this case apparently seemed to be an uncomplicated, independent, clinically complete insufficiency of the pituitary gland, without evidence of other glandular dyscrasia, marked effect would probably be expected from such administration of pituitary glandular substance of both lobes.

The obesity, which is usually the chief complaint in these bilobar groups of pre-adolescent hypopituitarisms, for which the patient applies for treatment, is not affected by the ordinary treatment for obesity. In the first place, it must be remembered that this is due to decrease in the general metabolism and the low sugar tolerance, and not to increase in the amount of food consumed. In fact, a great majority of these patients take comparatively small amounts of food, either naturally or through an acquired habit of dieting, yet continue to gain weight at an alarming rate. It is also true that they are not the large carbohydrate eaters so frequently found in hypothyroidism, in which the individual seems to have a peculiar desire for sweets and sugars. The authors have found, by careful questioning, that such patients are more inclined to be meat eaters, and ordinarily care very little for such articles of diet as bread, potatoes, sugar, starches, etc. Simple **dieting**, then, has very little effect, if any, upon their obesity. This is also true of other treatments ordinarily directed against obesity. Excessive elimination, such as **sweating, gymnastics, massage, exercise,** etc., has practically no effect upon the reduction of weight or localized adiposity. Unfortunately, the hypoplasia of the genitalia is a condition which receives very little attention or treatment, on account of its not being recognized as a hormonic sign at this early age. It is only after the pre-adolescent age or almost at the age of maturity that attention is first called to the non-development of these organs. Consequently, treatment is very rarely undertaken or diagnosis considered in order to determine the cause of a possible aplasia of this system. Fortunately, pre-adolescent types of this disease do not have the marked nervous or intracranial disturbances such as *headache, migraine, psychosis, epileptiform attacks, intrathoracic pressure symptoms,* or *gastro-intestinal disturbances,* which are usually associated with postadolescent inactivities of this gland. For this reason, it is very rarely that these conditions receive treatment before adolescence; but should such symptoms occur in these cases, ordinary treatment directed toward their relief is without benefit, whereas if beneficial effects do occur from **organotherapy** or possibly **surgical treatment** directed toward the pituitary body, these secondary symptoms usually disappear without additional treatment. The surgical indications in this type of hypopituitarism should be kept in mind, but delayed until other forms of treatment, particularly organotherapy, have been given prolonged trial. Remembering that there is no evidence in the above case that there is increased size of the pituitary gland, no definite objective signs of the increased general intracranial pressure, nor focal disturbances in the neighborhood of the pituitary gland at the base of the skull, one would be reluctant to advise surgical treatment directed toward this gland. In some of these cases operated upon by Cushing and others, however, a **decompressing trans-sphenoidal operation** has been done with benefit. "One of the first operations for hypophyseal tumor successfully performed by Eiselberg was upon the patient described by Froehlich. The operation was followed by the disappearance of the local symptoms due to the presence of the tumor, while at the same time there was an improvement in all the general symptoms which were attributable to the hypophysis. The weight fell, the obesity was reduced, hair grew at the pubes and in the axillæ, and sexual activity manifested itself by erections." The argument in favor of surgical treatment for these decreased secretions or inactive pituitary glands is that the simple decompression might possibly sufficiently relieve pressure upon the gland to allow it to become active again, provided its inactivity was due to pressure from its small bony encasement demonstrable by clinical and roentgenological examination. It must be borne in mind that in these cases in which all other treatments have failed, surgery is justifiable. In those cases in which there is definite enlargement of the sella turcica or other evidence of neighborhood pressure symptoms, surgical intervention should be attempted early, and the other treatment, **x-ray, radium,** and **organotherapy,** instituted as a postoperative instead of a pre-operative procedure.

Prognosis.—The ultimate prognosis in these cases is always unfavorable. So few in number have been known to react completely either to medical or surgical treatment, or to a combination of both, that a guarded prognosis should always be given. This pertains as well to reaction of individual complaints as to the ultimate outcome of the case. Many of the incomplete and partial forms of this disease have a long duration of life, and frequently die of other diseases. The susceptibility of those with hyposecretory diseases to other diseases has been noted in the introduction as of possible prognostic importance. Hypopituitarism, as well as hypothyroidism, is becoming very well known as a susceptible state to other infectious diseases. Lues is known to run an entirely different course, with prevalent early cerebrospinal lesions, in this type of individual. These obese types are particularly susceptible to a great many other infections, such as rheumatism, tonsillitis, bronchitis, etc. It has been our personal observation to note that this susceptibility is probably accounted for by the extremely low metabolic process, associated with subnormal temperature and poor dermal protection and radiation. Other characteristics noted in these cases are a certain psychic depression, a persistent fluffy type of hair, a thick, inelastic skin, persistence of the milk teeth, failure of closure of the epiphyses, and a delicate and underdeveloped condition of the skeleton.

Pathology.—The pathology in this particular disease referable to the gland is not definitely known in this case. The pathological changes of other systems of the body are of little significance, except those affected by the inactivity of the gland—the obesity, particularly affecting the mammæ, the abdominal wall, and the lateral portions of the thorax. It has also been noted that marked deposits of fat in the mesentery, the omentum, and the retroperitoneal spaces occur. The epiphyseal junctures of the skeleton are early united, in contrast to that which is found in eunuchoidism, in which these junctures remain open until late in life. The smallness of the bones of the head and the absence of development of the acral bones—inferior maxilla, carpal, metacarpal, phalangeal, and tarsal bones—both as to width and tuberosity projections, are indicative of this disease. The teeth, as was illustrated particularly in the above case, are of poor dentine composition, becoming soft and decayed almost as soon as the eruption occurs. This is present both in the primary and the secondary sets of teeth. The toothline in these cases, as well as in hyperpituitarism, is usually very straight and clean-cut, with no overcrowding, irregularity, or deciduous teeth appearing through the gums above the primary teeth. In some cases, there is slight separation of the upper incisors. There is no retardation of the ossifying centers of the carpal bones, as in early hypothyroidism (cretinism). The genital system is completely aplastic, the cells of Leydig or the interstitial cells of the testicles and of the ovaries are very scant and meager, and the graafian follicles and the seminiferous tubules of Sertoli remain in the infantile state of imperfect development. The uterus remains infantile in this type, as it does in the anterior lobe insufficiency in the pre-adolescent type of hypopituitarism.

In the majority of the cases personally observed—the unilobar and the bilobar—of pre-adolescent and postadolescent hypopituitarism, there was clinical evidence of hypothyroidism. There has been no associated pineal lesion noted. The blood shows, in the majority of the cases, lymphocytosis but no eosinophils. The skin has usually been thick and infiltrated, simulating somewhat the skin of pure hypothyroidism. These changes, in the majority of the cases, have been greatly relieved by thyroid treatment, demonstrating that the cause of the dermal changes was the associated insufficiency of the thyroid. In regard to the organs of special sense, in the above case the eye was not affected through pressure on the chiasm. The secretions of the gastro-intestinal tract were greatly modified. There seemed to be marked dryness of the skin, and frequent hypersecretion of the parotid gland, causing salivation. Certain rather constant changes were also seen in the parenchymatous organs, such as increased size of the colloid alveoli in the thyroid, an abnormally persistent thymus, fatty infiltration in the liver, and increased thickness of the adrenal cortex. Aschner regards the anterior lobe as mainly responsible for these changes. Goetsch has been able to confirm these findings in numerous instances.

B. Bilobar Insufficiency of the Postadolescent, Aneoplastic Type

Etiology.—The history of the following case (VIII) relates only two infectious diseases, mumps and pneumonia, and those occurred in early childhood. It is very unlikely that either of these had an etiological influence upon the hypopituitarism. There is no family history of any ductless gland dyscrasias. That this case was not due to pituitary neoplasm is demonstrated by the exceedingly small sella turcica and the absence of all intracranial pressure symptoms.

Symptomatology.—History: Case VIII.—Mrs. R. D., aged twenty-four, General No. 2384, St. John's Hospital, St. Louis, June 22, 1918.

Present.—Chief Complaints: (1) *Enormous obesity, gain in weight of 100 pounds during the past year.* (2) *Amenorrhea,* complete and continuous during the past year. (3) Attacks of *hot flushes,* followed by chilly sensation and cold sweats. (4) Continuous *pressure sensation in the head,* associated with dizziness. Daily attacks of compression pain in the vertex of the skull, most frequently present in the afternoon and evening. (5) *Nausea and occasional vomiting.* Frequent attacks of gaseous distention of the abdomen. The nausea and vomiting are not associated with the abdominal tympany. (6) Attacks of pain in the lower left side of the abdomen. This is sharp, shooting in character, not associated with urinary disturbances or affected by defecation. (7) *Rapid decay of the teeth.* In the past seven months, it has been necessary to remove four teeth.

Duration.—One year.

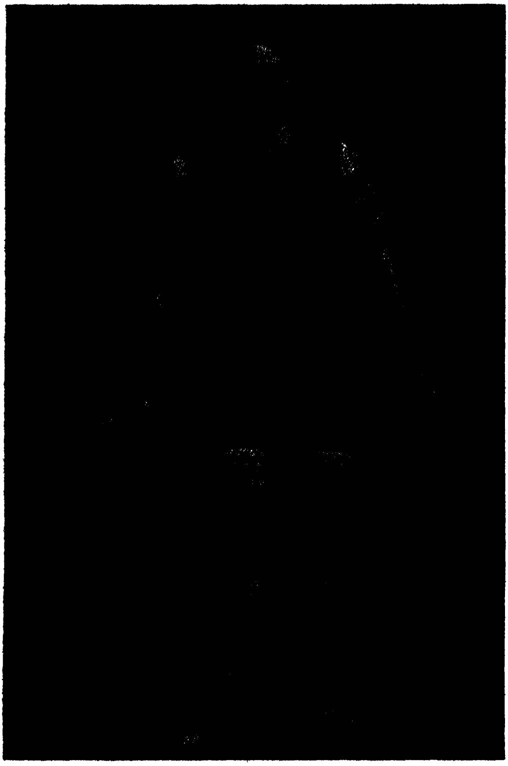
Course.—*Onset,* sudden. Until a year ago, the patient was in perfect health, having no symptoms referable to the head or abdomen, and no changes of figure or weight. The menses began at the age of fourteen, were of three days' duration, *always scanty, consisting of only a little flow for the first, and sometimes the second day, and very slight on the third.* The menses were usually slightly painful, but up to the age of the onset of the present trouble (age twenty-three) had always been regular. At the time of maturity, the patient weighed 98 pounds. From that time to the age of twenty-three, there was a gradual, slow gain of weight to that of 150 pounds. *One year ago, at the age of twenty-three, there was complete cessation of the menses.* A few months after this, the patient noticed that she began to *gain weight very rapidly,* and during the following year her *weight increased from 150 to 250 pounds.*

Progress.—Coincident with the beginning of the amenorrhea and the rapid adiposity, there occurred *severe attacks of headache, fullness in the head, vertigo, nausea, vomiting, gaseous distention of the abdomen, constipation, and shooting pains in the lower left abdominal quadrant.* She has never had any dyspnea, substernal pressure, palpitation, or urinary disturbances. Attacks of headache and various abdominal symptoms and signs have been present at variable intervals since the onset. They have occurred in numerous combinations, yet are considered by the patient as secondary symptoms, less important as compared with the enormous obesity. There has been no temporary or permanent change in the size of the hands, feet, or face. The patient perspires more freely now than formerly. Hot flushes, followed by cold sweats, have been one of the most distressing symptoms. The patient *was married at the age of fourteen, has had a tendency to frigidity, and has never conceived.* The amenorrhea has been absolutely complete and continuous from its onset one year ago. The obesity previous to her amenorrhea involved her entire body, with the exception of the backs of the hands and the neck. Since the cessation of her periods, *the gain in weight has been limited to a large extent to the hips, the lower portion of the abdomen, the upper thighs, and the mammæ.* There have been no fat cushions added to the dorsa of the hands, and at no time has there been enlargement of the fingers or toes.

Past.—Mumps, pneumonia. Operation nine years ago for "abscess of the stomach" (pelvic operation). The periods were not modified by this operation.

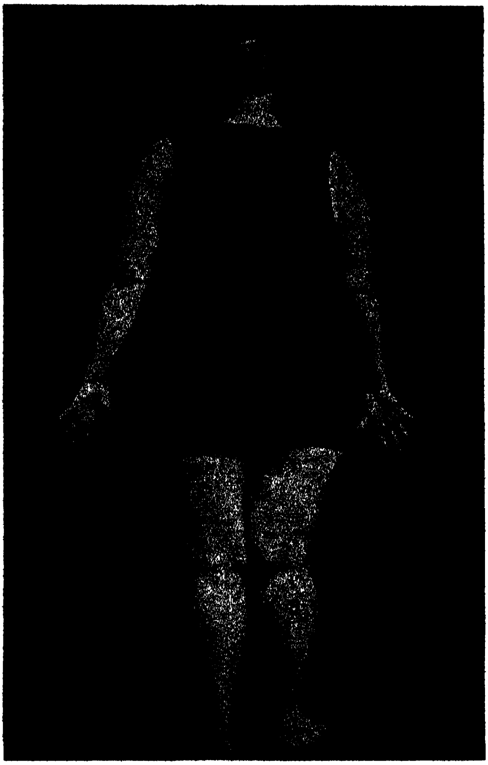
Personal.—Appetite good, bowels constipated, requiring cathartics, no urinary disturbances. Drinks tea and coffee moderately; no alcohol. Menstrual disturbance as given in the present history.

Family.—Father died of tuberculosis; mother, of cancer of the stomach. Eight brothers, five sisters living, well. One brother dead, accident. One sister died in infancy. Brothers and sisters all very tall, but not obese. Father and mother both were tall, but neither stout. Husband living, well. No family history of epilepsy, insanity, kidney, liver, or heart diseases.



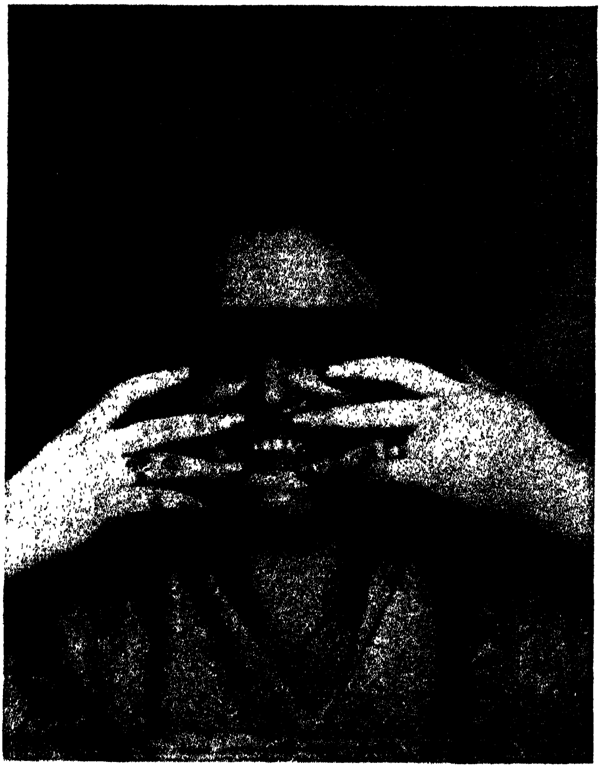
CASE VIII. FIG. 1.—NOTE MARKED OBESITY OF GIRDLE TYPE, INCLUDING ABDOMEN AND UPPER THIGHS, SHARPLY DELIMITED TO JUNCTURE OF MIDDLE AND LOWER THIRDS OF THIGH, AND COMPARATIVE SLENDERNESS OF LEGS, SMALL HEAD, HANDS AND FEET.

EXAMINATION.—*General.—Exceedingly obese woman, girdle obesity particularly marked. Excessive adiposity from the navel down to the junction of the upper and middle thirds of the thigh, where it stops abruptly,* so as to make a very deep indentation of the lower third of the thigh, which is fairly free from fat deposit. *Mammæ and mons very large.* Mammæ pendulous, made up mostly of fat, consisting of very little glandular tissue. *Upper arm has obesity from just above the shoulder to the lower third of the arm.* Forearms, hands, and legs not particularly obese. Backs of hands absolutely free from fat pads, so that the veins are distinctly seen and the bony markings made out. *Hands exceedingly small* compared with the rest of the body, rather wide; *fingers very short,* tapering from the distal phalangeal joints (size of glove, No. 6). Feet not particularly small, toes not unusually characteristic (size of shoe, No. 6½), no fat padding along the dorsa. *No distinct supraclavicular fat pads,* some universal obesity throughout the body, not particularly marked. No cuffing at the lower end of the arm, no demarcation of obesity at the ankle. *Small, girlish head, youthful face; nose of classical hypopituitary type,* bridge straight, small, but well proportioned to the rest of the face. *Pigmentation most striking and marked: marked chloasma about the forehead and mouth, with vitiligo about the lips. Brownish chloasma over the chin, extending up over the angles of the mouth, toward the malar processes, and down over the neck, with large and small spots of vitiligo. Considerable pigment over the entire body, of this same chloasmic character,* particularly marked on the abdomen, mammæ, and chest. *Throughout this diffuse*



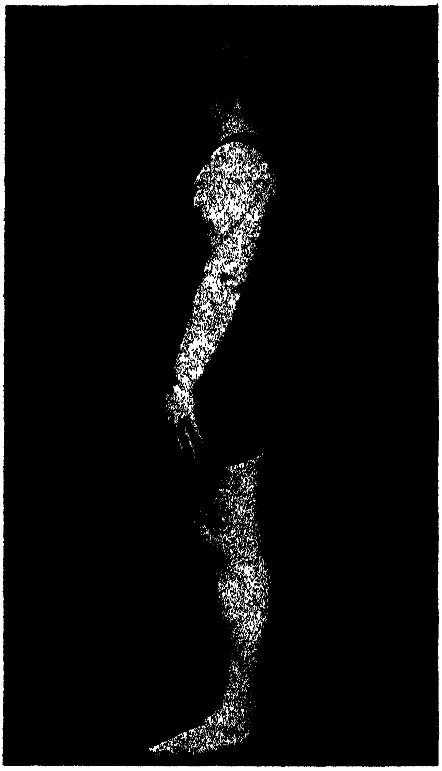
CASE VIII. FIG. 2.—POSTERIOR VIEW, DEMONSTRATING STRIKINGLY CHARACTERISTIC GIRDLE AND UPPER THIGH OBESITY.

chloasmic pigmentation are scattered large and small blotches of vitiliginous skin, which are entirely free from pigment. Pigment extends down the extremities, particularly on the forearm down to the wrist, where it changes into vitiliginous skin, *more marked on the extensor than on the flexor surfaces.* On the lower extremities, the pigmentation is not so marked; there are some enlarged veins, very slight pigmentation on the backs of the feet, also vitiliginous patches of skin entirely free from pigment. *No abnormal distribution of hair;* exceedingly slight lanugal hair anterior to the ears and over the upper lip, absolutely none on the chin. Practically no hair on the extremities, very slight amount in the axillæ and over the mons. No edema, cyanosis, or dyspnea. No abnormal gait, station, or position. Skin slightly thickened, slight infiltration of subdermal tissue. This is more marked over the adipose areas than where there is no obesity. For instance, over the backs of the hands, where the skin is thin, there is absolutely no subdermal infiltration. Color exceedingly good, mucous membranes well colored, pigmentation as noted above. Pulse-rate, 80-88, regular, equal, symmet-



CASE VIII. FIG. 3.—NOTE SMALL HANDS, TAPERING CHARACTER OF FINGERS, YOUTHFUL FACE, AND SMALL CANINES.

rical, low volume and tension, no special type. Temperature, 98°-98.4° F. (36.6°-36.8° C.). Temperament psychoneurotic, exceedingly well controlled. Weight, 250 pounds. Measurements: Height, 5 feet 9 inches (175 cm.); from vertex to symphysis, 34 inches (86 cm.); from symphysis to soles of feet, 35 inches (89 cm.); humerus, 13½ inches (34 cm.); forearm, 11 inches (28 cm.); femur, 18 inches (46 cm.); leg, 17¼ inches (44 cm.); circumference of head, 21¼ inches (54 cm.); superior maxilla, 19½ inches (50 cm.); neck, 14½ inches (37 cm.); bust, 45 inches (114 cm.); at navel, 41 inches (104 cm.); hips, superior spine, 51 inches (130 cm.); upper thigh, 32 inches (81 cm.); at junction of middle and lower thirds, 22 inches (56 cm.); calf, 15½ inches (39 cm.).



CASE VIII. FIG. 4.—LATERAL VIEW, DEMONSTRATING CHARACTER OF GIRDLE OBESITY.

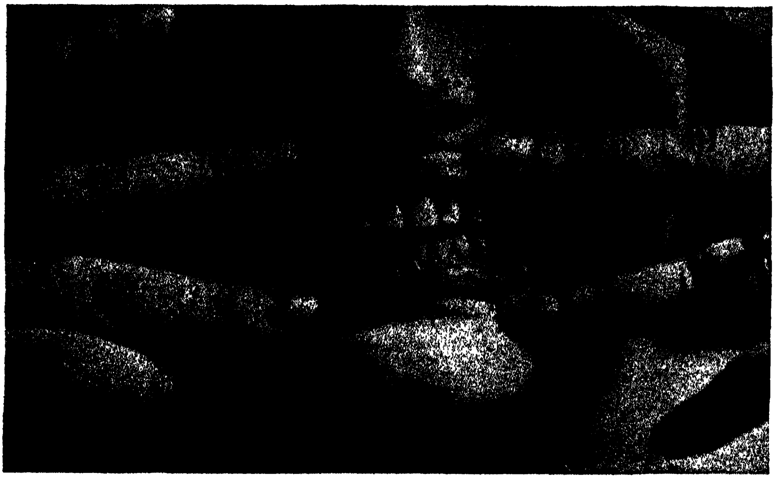
Regional (Positive Physical Signs).—*Mouth:* Separation of the upper incisors, canines very small; considerable number of teeth absent. *Chest:* Lungs and pleuræ negative. *Heart:* Normal. Blood-pressure: Systolic 150, diastolic 90. *Abdomen:* Obesity in the lower half, as noted above; abdominal viscera negative.

LABORATORY FINDINGS.—*Urine.*—(*a*) Catheterized specimen, color lemon, specific gravity 1.008, reaction acid. Trace albumin. Dextrose, leukocytes, erythrocytes and casts negative.

(*b*) Twenty-four-hour specimen, pale, faintly alkaline in reaction. Faint trace albumin, few leukocytes. Dextrose, erythrocytes and casts negative. Epithelial cells present.

(*c*) Twenty-four-hour specimen, 500 c.c., color straw, specific gravity 1.023, reaction acid. Albumin, dextrose, erythrocytes and casts negative. Leukocytes 30 to high power field, many epithelial cells.

(*d*) Twenty-four-hour specimen, 700 c.c., color straw, specific gravity 1.015, reaction acid. Trace albumin, numerous leukocytes. Dextrose, erythrocytes, and casts negative.



CASE VII. FIG. 5.—NOTE MARKED TAPERING OF FINGERS AND SLENDER, DELICATE NAILS, SEPARATION OF UPPER CENTRAL INCISORS, AND SMALL LATERAL INCISORS AND CANINES.

Feces: Two specimens, brown, soft. Mucus, pus, ova, parasites, and occult blood negative.

Stomach Contents.—Ewald test-meal, normal in odor, whitish, well chymified. Free hydrochloric acid 47, combined acidity 75, mucus positive, lactic acid negative, bacilli and blood negative.

Blood:

Erythrocytes	5,440,000
Leukocytes	5,200
Hemoglobin	108 per cent.
Wassermann	negative

Differential analysis:

Neutrophilic leukocytes	52	per	cent.
Basophilic leukocytes	1	"	"
Eosinophilic leukocytes	1	"	"
Large lymphocytes	24	"	"
Small lymphocytes	22	"	"

Sugar Tolerance Test:

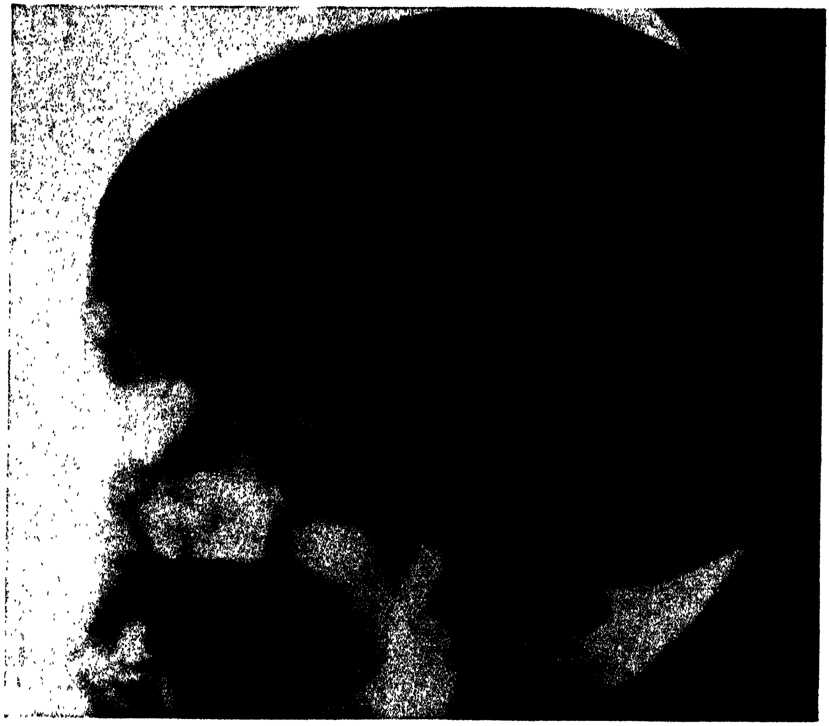
(*a*) Blood-sugar (following 14-hour fast) 0.054 per cent.
(*b*) Blood-sugar (two hours later, following ingestion of 199.84 grams [7 ounces] dextrose by mouth).....0.060 " "

Special Examinations.—*Fluoroscopic.*—*Head, neck, chest, heart, vessels, diaphragm, stomach,* normal.

Trochoscopic.—Spasticity of the descending, iliac, and pelvic colons, remainder of the colon normal.

Roentgenogram of Skull.—Slightly increased anterior-posterior diameter. Sinuses small. *Sella turcica small,* especially clear-cut.

Diagnosis.—This is a typical case of *dystrophy adiposogenitalis* (*bilobar hypopituitarism, postadolescent variety, aneoplastic type*). It is described at this time on account of the marked similarity to the previous case (VII). It differs from this case *in sex* and in that *its time of occurrence is after adolescence.* It contrasts well with Case VII in that it shows the difference of skeletal growth in cases occurring before and after maturity. Case VII, occurring before maturity, has a marked retardation of long, short, and flat bones, whereas this case, occurring at the age of twenty-two, has no evidence of undergrowth of the long bones, but displays classical hormonic signs in the short, flat, and peaked bones, as shown by the small head, the typical small, pointed pituitary nose, the small hands, with tapering fingers, the small feet, etc. The effects upon the genitalia are quite decided in both cases, differing only in time of occurrence. In Case VII, in which the anterior lobe secretion was withdrawn before adolescence, the genitalia remained infantile. In this case, in which there was a sudden insufficiency of this lobe at the age of twenty-two, after the genitalia had been developed and functionating for eight years, the uterus was found to be of normal size, and until the age of twenty-three the periods were present, although of imperfect type, being of only three days' duration and markedly decreased in amount of flow. There probably was no insufficiency of the posterior lobe of the hypophysis until a comparatively short time before the onset of the complete amenorrhea, although it is probable that there was a gradual decrease of secretion from this lobe, as has been evidenced by the gradual increase of weight, previous to the complete cessation of the menses. At the age of twenty-three, when the amenorrhea commenced, it is likely that the posterior lobe became decidedly inactive, as there was a sudden onset of extremely rapid increase in obesity, consisting of a gain of 100 pounds during the past year. All the hormonic signs indicating marked inactivity of both the anterior and the posterior lobes are present in this case. At the time of observation, the posterior lobe insufficiency signs differ very little from those of Case VII. Both of these cases are comparatively free from constitutional symptoms, such as headache, dyspnea, nausea, and lumbago. There is no evidence of uncinate pressure or other intracranial pressure effects in either case. In this way they both contrast very markedly with the posterior and the bilobar insufficiencies which occur later in life, usually associated with incapacitating constitutional symptoms. That the patient was married at the young age of fourteen might possibly have had something to do with stimulating the activity of the anterior lobe and delaying to a certain extent the insufficiency of this lobe to the age when it occurred, at twenty-three. The extent and amount of obesity seems to depend to a certain degree upon when the inactivity of the posterior lobe occurs. In nearly all of the personal observations of the writers in which there was a primary insufficiency of this lobe early in life, the obesity was very extreme. The

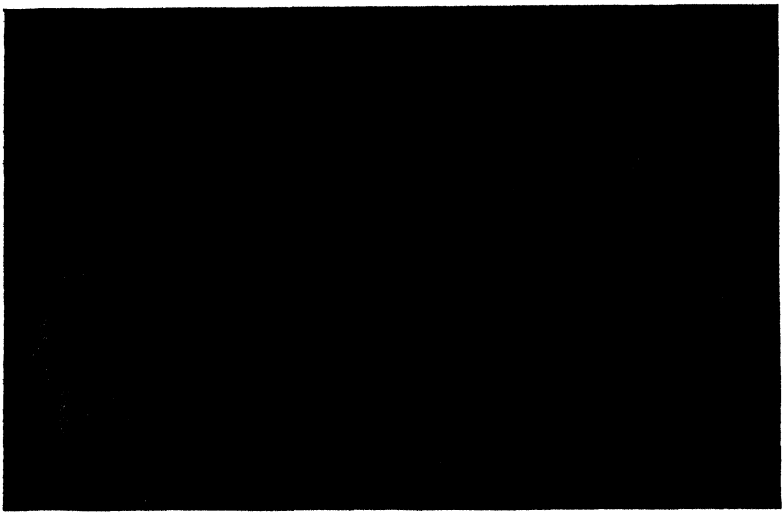


CASE VIII. Fig. 6.—Note Small Sella Turcica.

amount is usually decidedly more in the female than in the male, and it has been noticed that in the married female it is more enormous than in the unmarried. In most of these cases, as can be seen, the obesity was of an extreme type, more marked in the female than in the male, and it was more marked in this case than in the cases described later (X, XI, and XII) occurring in the adolescent age. Two of these patients are not married. Both show the very marked carbohydrate tolerance, the slow pulse, the subnormal temperature, the low blood-pressure, etc., so characteristic of hypopituitarism in general.

Complications, Sequelæ, and Associated Diseases.—The complications, sequelæ, and associated diseases have not been marked in this case. This corresponds well with the character of the group complex, which is more inclined to be less susceptible to infectious diseases than that occurring in the late adult life.

Clinical Varieties.—These 2 cases (VII and VIII) have been selected as good illustrations of the clinical variety called *pituitary obesity*. Both are good examples of Fröhlich's disease of dystrophy adiposogenitalis. Case VII, however, which has a typical aplasia or complete absence of development of the genitalia, would probably fit this picture of Fröhlich's disease more decidedly than Case VIII, which occurred at the age of twenty-two, after the genitalia were properly developed and had been functionating, at least partially, for almost nine years. The size of the uterus in this case (VIII) was found to be normal; and if this same deficiency of the pituitary had occurred at the same time (age of twenty-two) in a male, there would probably have been a normal-sized testicle and penis. For this reason, this term designated by Fröhlich, when applied to the postadolescent cases, is slightly confusing in that the individuals so classed do not have the miniature, infantile genitalia present in the same type of cases previous to maturity. Besides the already well described obesity which is the presenting sign and the most discomforting chief complaint of the patient in this case (VIII), a very good example is afforded of *the abnormal pigmentation, on account of the extreme amount and extent of chloasmic impregnation of the skin presented in this individual case.* Pigmentation associated with endocrinous glands has been assigned almost entirely by all authors to either primary or associated disease of the adrenal cortex. *The writers wish to take exception to the adrenalogenic origin of pigmentation present in pituitary diseases.* This is done upon the basis that in almost every case of hypopituitarism in which there was other hormonic evidence of involvement of the anterior lobe of the pituitary gland, positive pigmentation was found. *In a great majority of these cases, and in this one particularly, there was absolutely no other clinical evidence of involvement of the cortex of the adrenals.* As illustration, there were no changes in blood-pressure, vasomotor disturbances, myasthenia, loss of weight, diarrheas, or other gastro-intestinal symptoms, which would speak for insufficiency of the adrenal. This same marked pigmentation has been observed in a few other cases of hypopituitarism, in which the writers have obtained very good results by substituting anterior lobe substance of pituitary gland. *In these cases they have noted very decided and rapid removal of this pigment, coincident with the actual decrease in the size and puffiness of the hands and the face and the relief of other symptoms,* such as abdominal pain, distention, etc., *after giving these patients hypodermic treatment of anterior lobe extract.* The writers have one patient under observation now in whom the pigment, which is quite marked previous to hypodermic treatment, is relieved almost completely within a few days following a single injection of anterior lobe extract. The puffiness and coarseness of the features of the face, and the swelling and sweating of the hands and feet are just as decidedly affected in this individual by the same treatment. No such rapid and transient removal or deposit of adrenalin pigment has ever been noted or referred to in reports of cases in literature, within the knowledge of the writers.



CASE VIII. FIG. 7.—NOTE MARKED CHLOASMA PIGMENTATION ABOUT NECK AND UPPER CHEST.

On account of its diagnostic value as a definite hormone from the anterior lobe of the pituitary, a more detailed description of this pigmentation will probably not be out of place. In nearly all cases of hypopituitarism there is a certain amount of pigment or slight yellow to golden chloasmic infiltration present. This is located in nearly all the cases across the forehead just below the hair line, on the lateral aspects of the temples, and at the angles of the jaw, going down the lateral aspects of the neck beneath the ears. It is frequently so faint and difficult to define that the patient must be placed in the proper light, and the hair raised back from the forehead so as to bring out the demarcation of the normal and impregnated skin. The next most frequent locations are the eyelids, around the angles of the mouth and on the upper lip. In addition, it may occur around the mammæ, extending beyond the areola of the nipple, and is occasionally seen in small chloasmic spots scattered over the chest and abdomen. It is usually intensified by exposure to the sun, and for this reason is more readily seen in the summer than during the winter months. It varies considerably with the periods, pregnancy, and the menopause. In certain cases it has been repeatedly observed to become very much intensified a few days previous to and during the period, and it occurs in a large majority of normal individuals during pregnancy, at which time it is usually not limited to the forehead, but present around the eyes, the angles of the mouth, the areolæ, etc. The presence of this pigmentation during pregnancy would agree absolutely with the marked hyperplasia of the anterior lobe of the pituitary gland, which has been demonstrated to be present at this time by Erdheim and Stumme. In Case VIII, herewith described, it occurred diffusely over the entire

CASE VIII. FIG. 8.—NOTE SMALL HAND, ABSENCE OF CUFFING AT WRIST, TAPERING FINGERS, AND MARKED CHLOASMA PIGMENTATION AND VITILIGO ABOUT FOREARM.

body, covering even the extensor surfaces of the arms down to the wrists, and was quite distinctly found on the lower extremities. Vitiliginous spots, skin that was entirely free from pigment, were found scattered throughout the chloasma in this case. The writers have really no other contention for attributing this pigmentation to the anterior lobe of the pituitary, with the exception of their clinical experience, which has found it associated almost exclusively with pituitary diseases which were not, as far as they were able to determine, related with either primary or secondary diseases of the cortex of the adrenals. The actual source, however, of this pigmentation is yet undecided. The writers have injected this theory probably upon insufficient basis at this time, in order to have other investigators, both clinical and experimental, by more extended observation, actually determine its value. If it does prove a sign indicating insufficiency of the anterior lobe of the hypophysis, it certainly will be of considerable diagnostic value, for the reason that it is such a common and fairly easily recognized clinical manifestation. It will be very interesting to observe the effect of treatment upon the pigmentation in this individual case; for, if it should be decidedly modified by the substitution of pure anterior lobe pituitary extract this would probably aid considerably in confirming the writers' theories concerning its origin.

Nothing further can be added by the writers of this article to the original descriptions, by Fröhlich, Bartels, and others, of this remarkable clinical group. This clinical variety is described here and classified under the anatomical classification of the typical bilobar hypopituitarisms, one of the pre-adolescent (Case VII), and one of the postadolescent (Case VIII) variety. The writers deem it essential to separate the clinical varieties of these diseases completely from the anatomicophysiological classification which they have provided, in the Introduction (General Classification, page 342). This is necessary because each variety and type of the insufficiencies of the hypophysis, as anatomically classified, has a large number of cases which can be grouped in classes on account of the marked similarity of their clinical pictures. It is true that nearly all of the bilobar insufficiencies of the hypophysis occurring before adolescence primarily as such (that is, not secondary to a hypersecretion of the posterior lobe of the hypophysis) have the obesity and the hypoplasia of the genitalia as the cardinal signs of their clinical syndrome. This is true because it is the extreme exception to have an inactive involvement of the posterior lobe alone, not combined with an anterior lobe insufficiency. In other words, whenever the posterior lobe is markedly deficient in secretion, there is usually an anterior lobe inactivity. This does not hold true with regard to the anterior lobe insufficiencies; that is, they are not always combined with the posterior lobe hyposecretions. Cases I, II, III and IV, described in the preceding sections, demonstrate that the anterior lobe may be underactive in its secretion or in its function, without any posterior lobe involvement. As has been shown in Cases V and VI, when this insufficiency of the posterior lobe occurs as a terminal condition following a hyperactivity of this lobe, the typical *obesity*, considered a necessary hormonic sign of inactivity of the posterior lobe, *is absent*. On account of this well-known symptôm-complex as the established standard for the diagnosis of hypopituitarism, it is necessary that the above differentiations be definitely understood. The proper understanding of the differences in the clinical and the anatomico-physiological classifications of these diseases will undoubtedly lead to more accurate diagnosis and therapeutic indications. With these 2 cases as classical pictures of bilobar insufficiency occurring before and after maturity, other clinical varieties of this type will be described in group series in the following sections. It is to be borne in mind that the following cases (with the exception of XVII, XVIII, and XX, which are anterior lobe insufficiencies), from IX to XXIII, are bilobar hypopituitarisms. They have been grouped into different clinical classes, on the basis that a certain number of them have the same presenting symptom or complex of chief complaints for which they constantly seek relief. And it is usually these chief complaints which are presented to the physician frequently in a very misleading way, so as to direct him to diseases of other organs which have been affected only secondarily through peculiar hormonic effects from the pituitary gland. It is thought that if these clinical varieties presenting the cardinal symptoms can be used as group illustrations in which diagnosis deductions are drawn from the most distressing symptoms of the pituitary gland leading to pituitarism, considerable scientific interest, as well as clinical investigation, will be stimulated toward closer insight and an effort to recognize all the hyposecretory varieties of the hypophysis.

Treatment, Prognosis, and Pathology.—The treatment, prognosis, and pathology of this case differ in no details from those of Case VII, a pre-adolescent variety of bilobar pituitary insufficiency.

ADDITIONAL OBSERVATION SINCE THE ABOVE CASE WAS REPORTED.—The patient was given **anterior lobe pituitary gland,** grains ii ss (0.16 gram) three times a day, after meals, during one week's observation in the hospital. She was given **pituitrin** (extract of posterior lobe and infundibulum) subcutaneously, beginning with 5 minims (0.3 c.c.) and increasing 5 minims (0.3 c.c.) daily until "general reaction" was produced. This did not occur until a dosage of 30 minims (1.9 c.c.) was given subcutaneously. After this dosage, the patient had a classical general reaction, consisting of marked general weakness, tendency to syncope, pallor, and tremor. Within five minutes after each injection severe abdominal cramps occurred, followed within ten minutes by a large defecation. The patient then left the hospital. On July 6, ten days following her discharge from the hospital, the patient returned for observation. Since leaving the hospital, she had received no pituitrin, but continued to take anterior pituitary gland in doses of grains ii ss (0.16 gram) three times daily for one week. The menses appeared three days previous to this date. *This was the first evidence of a period for over a year.* The duration of the period was two days and the flow on each day was scanty, requiring only two menstrual pads. It was associated with considerable dysmenorrhea. There was no loss of weight, change in measurements, or perceptible effect upon the pigmentation. It must be remembered, however, that the treatment to this date consisted of only seven injections of pituitrin and two weeks' treatment of anterior lobe of pituitary gland, consisting of a dose of grains ii ss (0.16 gram) three times daily.

SECTION 6

PITUITARY HEADACHE

(*Bilobar Insufficiency of the Postadolescent, Aneoplastic Type*)

Etiology.—No etiology in the form of trauma, hereditary ductless gland dyscrasias, or infectious diseases, is present in this case.

Symptomatology.—History: Case IX.—Dr. M. L. J., Alton, Ill., aged thirty-one, General No. 2521, St. John's Hospital, St. Louis, June 4, 1917.

Present.—(*a*) *Chief Complaints:* (1) *Migraine complex,* hemicranial in type, shifting frequently from one side to the other, accompanied by nausea, vomiting, and occasional visual disturbances, in the form of scotomata, rings, dots, and circles. (2) *Albuminuria, transient polyuria, high blood-pressure, diminution of sight.* (3) *Slight edema of the calves of the legs* at times. (4) *Transient attacks of mental confusion,* without complete loss of consciousness, followed by *nausea, vomiting, and headache.* Two of these attacks occurred, the first one a year ago. Tendency to *mental slowing, retardation of ideas,* difficulty of concentration of mind. Some trouble in correlation of words and sentences, attributed more to lack of interest, to feeling of "don't care," "too much trouble." Loss of interest in ordinary affairs and even in business, which was of greatest concern. Some memory defect. No marked tendency to drowsiness. Some slight increased tremor of the hands at times. No cardiac palpitation. (5) *Rapid increase in weight,* extending over the past nine years. At the age of twenty-two the patient weighed 145 pounds, three years later, 190, and a year or two after that, 238. This distribution of fat had a tendency to girdle obesity particularly, with prominence of the lower abdomen and hips. There has been an increase of five or six inches in the waist, and two in the bust. *Marked change in the contour of the face, striking difference in facial expression in that same length of time, being a heavier cast of countenance at the present time.* (6) There has been marked *loss of pigment in the hair,* no marked changes as far as dryness, breaking, falling out, etc., are concerned. Decided *brownish pigmentation about the face, forehead, and cheeks, and on the lateral aspects of the neck;* no marked pigmentations elsewhere. Decreased tendency to perspiration. Change in the texture of the skin, patient stating it feels "leathery," some tendency to dryness, no marked cracking or desquamation. (7) Some tendency *to increased constipation.* (8) Severe *dysmenorrhea.*

Duration.—The condition has lasted for seven years.

Course.—*Onset,* insidious. Seven years ago, the *headaches* became severe. They were usually of the migraine type, hemicranial, or shifting in location, accompanied by nausea, vomiting, and scotomata.

Progress.—Until a year ago, the headaches came on with increasing frequency, reaching a maximum of once a week, bearing no distinct relation to periods, not being increased in severity at that time. The adiposity dates back nine years, to the patient's entrance into the university. During the three years of school, she gained 45 pounds in weight, and within a year or two following graduation, 45 pounds more, increasing in weight within four or five years *from 145 to 238 pounds,* this obesity being deposited in the region of the lower abdomen and the hips, accompanied by pigmentations and dermal, nervous, and mental manifestations, as described under Chief Complaints. There has been no marked decrease in secretions, with the exception of perspiration. *The urinary output has been somewhat increased. The patient states that particularly before one of these headaches, it becomes a real polyuria.* The patient has been concerned about the kidney function; and in support of kidney disturbance, there have been a high blood-pressure (ranging from 200 to 164 systolic, according to the present reading), some slight dyspnea after exertion, albuminuria, and a doubtful edema. These later clinical manifestations, namely, headache, polyuria, albuminuria, high blood-pressure, and ocular symptoms, led her physician to the diagnosis of nephritis, for which she was referred. (For subsequent course since patient's discharge from hospital, *see* under Treatment.)

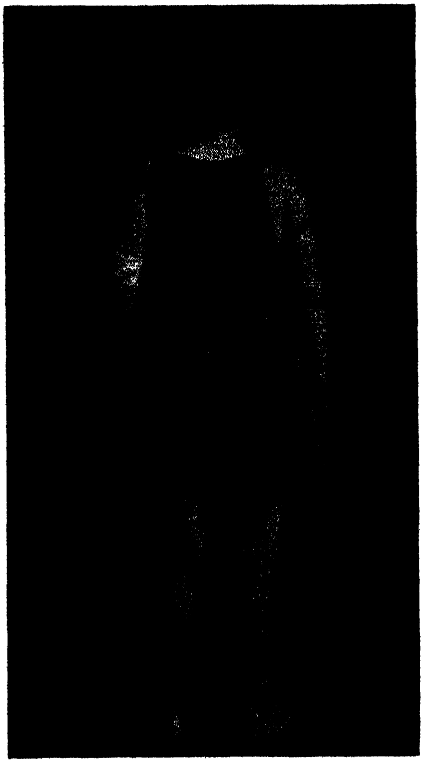
Past.—Malaria, no frequent severe tonsillitis, operations or injuries.

Personal.—Tea and coffee moderately, no alcohol. The menses began at the age of eleven, marked dysmenorrhea, associated with migraine and gastric disturbances, nausea, vomiting, etc. Appetite good, occasional short attack of insomnia, bowels constipated.

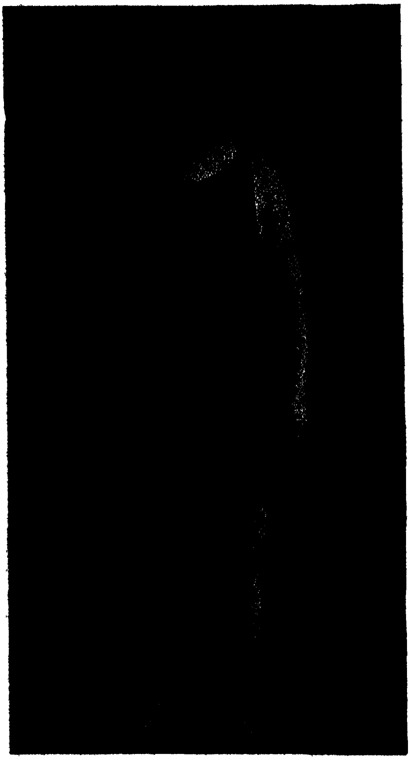
Family.—Father living, aged sixty-nine, well. Mother dead, aged nineteen, congestion of the brain. Father had migraine. No family history of tuberculosis, cancer, liver or kidney trouble, goiter or ductless gland dyscrasias.

EXAMINATION.—*General.*—Obese individual, 5 feet 6 inches tall. Adiposity is universal, with the exception of fat padding on the dorsa of the hands and over the arches of the feet. *Classical girdle obesity* present, to which is added *supraclavicular and posterior cervical padding.* Abdomen large, thick-walled, arranged in fat folds. Mammæ extremely well developed, pendulous, large. *Hands and feet unusually small;* head fairly well proportioned to the rest of the body. Color of exposed surfaces bronzed, unexposed surfaces normal, pigmentation about the waistline from pressure and irritation of the corset, slight pigmented ring around the abdomen. *Chloasmic spots about the forehead and malar prominences, slight chloasmic blotching at the angles of the jaw and down the lateral aspects of the neck.* Skin diffusely hyperemic, subjected to vasomotor changes from pressure or irritation. No edemas or varicose veins. No abnormal gait, station, or position Pulse, slow, regular, equal, symmetrical, increased in pressure and vol-

ume. Temperature, 98°-99.8° F. (36.6°-37.6° C.); respiration, 22-24 (three days' observation). Temperament highly psychoneurotic. Blood-pressure, systolic 165, diastolic 95. Measurements: bust, 46 inches (117 cm.); neck, 14 inches (36 cm.); waist, 38½ inches (98 cm.); hips, 58½ inches (149 cm.); upper arm, 14 inches (36 cm.).

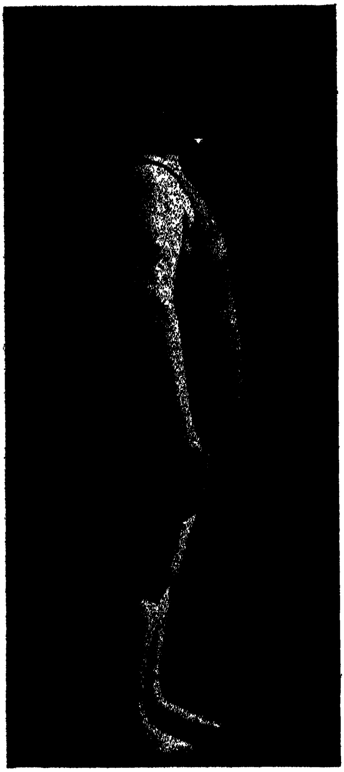


CASE IX. FIG. 1.—NOTE CLASSICAL GIRDLE AND UPPER THIGH OBESITY, RELATIVE SLENDER CHARACTER OF LEGS, AND SMALL HANDS AND FEET.



CASE IX. FIG. 2.—ANTERIOR VIEW.

Regional (Positive Physical Signs).—*Eyes:* Pupils slightly unequal, left larger than right, react to light and accommodation; eye-muscles intact, no lagophthalmos, no Stellwag's sign, palpebral slits equal, no increased tension or protrusion of eyeballs; scleræ clear, lids negative. *Mouth:* Lips thick; toothline very straight, separation of upper incisors, no overcrowding of lower anterior teeth. *Neck:* Thyroid—very slight enlargement of the right lobe and isthmus, not vascular, no pulsation or bruit. *Chest:* Lungs, pleuræ, negative. *Heart:* Apex-beat in the fifth interspace, at about the interclavicular line, circumscribed, not particularly forceful or wide; no diastolic shock, thrill, rub, or bruit palpable. Heart borders: Apex-beat, fourth rib, right sternal border. Sounds: Apex, *systolic murmur* transmitted to the anterior axillary line, *decreased to a considerable extent by deep inspiration, but not obliterated entirely; same murmur heard over the whole precordia.* This murmur over the pulmonic area *disappears entirely on deep inspiration, also over aortic;* second aortic only slightly accentuated, transmitted up from the aortic area to the jugulum; no tit-tat sound or roughening; no other abnormal findings over the large vessels of the chest or neck. *Abdomen:* Viscera negative. *Extremities:* Partake in the general obesity, no false or true edema; bones and joints negative.



CASE IX. FIG. 3.—LATERAL VIEW.

Hands small, pituitary type, free from dorsal padding; feet small, arches high, free from fat padding. *Reflexes,* normal.

LABORATORY FINDINGS.—*Urine.*—(*a*) Single specimen, cloudy, pale, specific gravity 1.010, reaction acid, dextrose negative, *albumin definite trace, few leukocytes and fine granular casts,* erythrocytes negative.

(*b*) *Catheterized specimen,* pale, specific gravity 1.004, acid, dextrose negative, *albumin definite trace, few leukocytes and fine granular casts,* erythrocytes negative.

(*c*) Twenty-four-hour specimen, 1,800 c.c., pale, specific gravity 1.006, acid, dextrose negative, *albumin* 0.75 *gram, few fine granular casts,* erythrocytes and leukocytes negative.

(*d*) Twenty-four-hour specimen, 1,725 c.c., pale, specific gravity 1.006, acid, dextrose negative, *albumin definite trace, few fine granular casts,* erythrocytes and leukocytes negative.

Feces.—Following blood-free diet, brown, formed. Mucus, pus, ova, parasites, and occult blood negative.

Blood:

Erythrocytes	4,650,000
Leukocytes	11,200
Hemoglobin	101 per cent.
Wassermann	negative
Stained smear	absolute increase of small lymphocytes

Chemical Blood:

Creatinin	1.50 mgms. per 100 c.c.

Functional Kidney Test (Phthalein):

Time of appearance	9 minutes
1st hour	13 per cent.
2nd hour	5 per cent.

Special Examinations.—*Fluoroscopic.*—Sinuses, thyroid, lungs, heart, vessels, mediastinum, diaphragm, thymus region, free from abnormal opacities.

Roentgenogram of Head.—Sella turcica normal, mastoid cells shown very plainly. Frontal sinus and antrum free from shadows. Sphenoid and ethmoid show many compartments and partitions. No abnormal shadows.

Diagnosis.—The diagnosis of this case is *hypopituitarism, associated with a secondary hypothyroidism.* The hypopituitarism consists of *bilobar involvement, postadolescent variety, not associated with neoplasm* of the pituitary gland. The hypothyroidism is evidenced in the universal obesity, to which is added supraclavicular and posterior cervical fat padding. The mimic nephritic syndrome, consisting of polyuria, albuminuria, casts, a low kidney function, a high blood-pressure, and visual disturbances, is undoubtedly due to the hypothyroidism. While there is considerable evidence connecting all of the patient's hormonic signs and symptoms with the insufficiency of these two glands, *the most important proof bearing upon the diagnosis is the therapeutic effect obtained from the administration of glandular substances of these two organs.* The fact that all of the patient's hormonic symptoms were not completely relieved by thyroid therapy, but that those thought to be due to renal disease (high blood-pressure, albuminuria, casts, kidney function, etc.) were relieved by thyroid-gland treatment, proves conclusively that they, as well as other hormonic signs thus relieved, were due to secondary secretory insufficiency of the thyroid. The further fact that the extreme headache, the attacks of nausea and vomiting, the nervous irritability, and the mental and psychical phenomena *not affected by thyroid, nor by corpus luteum medication, were finally completely relieved by the addition of anterior lobe pituitary extract,* shows that more than probably *the insufficiency of this lobe of the pituitary gland was the causative factor of these hormonic signs and symptoms.*

The physical signs bearing upon the diagnosis of anterior lobe insufficiency in this case, are those referable to the shape and size of the head, the separation of the superior incisors, and the extremely small and typically pituitary hands and feet. The dysmenorrhea alone could not be considered evidence of the inactivity of the anterior lobe of the hypophysis. The fact, however, that it was completely relieved by anterior lobe extract, tends to the conclusion that the hyposecretion of this lobe was its cause. The physical signs indicating hypothyroidism were those above noted, relative to the subcutaneous deposition of fat about the neck, arms, legs, posterior thorax, etc. Besides this obesity, there was a slight enlargement of the right lobe of the thyroid gland, and a typical thyroid heart. The temperature, ranging slightly above

CASE IX. FIG. 4.—SMALL SELLA TURCICA.

normal in this case, from 98° to 99.8° F. (36.6° to 37.6° C.), is difficult to explain. The pulse was not characteristically slow, as is usually found in hyposecretory diseases of the hypophysis and the thyroid. The absence of an enlarged sella turcica or other intracranial pressure symptoms groups this case with the aneoplastic types of pituitary disease.

The DIFFERENTIAL DIAGNOSIS necessary to consider in this case is, first, that of cardiorenal disease, on account of the presence of objective signs of cardiac and renal lesion; second, that of myxedema as a cause for the entire symptom-complex. Cardiorenal disease can be excluded as a primary, or even a secondary cause for the patient's clinical complex, on the basis that all of the so-called renal symptoms were relieved absolutely by simple thyroid therapy. Myxedema, while it will explain the renal and cardiac manifestations, can be excluded as the independent disease producing all the symptoms, by the fact that the most distressing symptoms and signs of the patient were not relieved by thyroid treatment forced to tolerance. That there was a secondary thyroid insufficiency in this case, as previously stated, has been proven by the fact that some of the signs and symptoms were completely, and others partially, relieved by thyroid medication. The fact that it was necessary to use anterior lobe pituitary extract to relieve additional incapacitating hormonic signs not affected by the proper substitution of thyroid and ovarian secretions, adds to the conclusion that both lobes of the hypophysis were the primary seat of disease.

Complications and Sequelæ.—The complications and sequelæ in this bilobar insufficiency of the anterior lobe of the pituitary were notably the secondary thyroid insufficiency, with the production of a combination of hormonic signs and symptoms which are very different from those resulting from an uncomplicated bilobar inactivity of the hypophysis. The marked changes in the renal output, in both quality and quantity, with the coincident rise in blood-pressure and ocular disturbances, are complications which are present more frequently in primary hypothyroidisms than in secondary hypothyroid insufficiencies to the diseases of the pituitary gland. The cardiac changes evidenced by a systolic murmur over the cardiac apex and the accentuated second aortic tone, were also undoubtedly due to the decreased thyroid secretion, and not to the pituitarism. The fusing of the two types of obesity—the typical girdle, mons, and mammary adiposity, with the cervical and universal obesity—adds to difficulties in diagnosis. The extreme changes in the mentality were so alarming to this patient that since her recovery she has frequently admitted her previous fear of becoming insane; which demonstrates that this complication is one that has a marked relation to the wide field of psychiatry. That these cases soon drift into very serious and irremediable dyscrasias, there is no doubt. The fact that they simulate other well-known diseases so closely allows them to be misinterpreted, and consequently mistreated, under the diagnosis of nephritis, myxedema, etc., which adds to the danger of their progression to serious conditions.

Clinical Varieties.—The purpose of the detailed report of this case is to use it as a means of describing *pituitary headache,* which was the most distressing and alarming symptom among the chief complaints. A review of the other cases reported in this series will demonstrate that nearly all the posterior lobe insufficiencies, the bilobar cases, and the anterior lobar inactivities associated with hypothyroidism, complain most bitterly of some form of headache. It has been only those primary decreased secretory pituitarisms of the anterior lobe which have not been associated with either a posterior lobe involvement or diseases of other ductless glands, which are comparatively free from pituitary headache; and even the pure anterior lobe diseases which are due to neoplastic changes have the headache of intracranial pressure. The term, *pituitary headache,* as used in this description, however, *does not refer to the type of headache caused by neoplasm of the pituitary or other brain tumors,* for the reason that *this headache is found present in many cases free from any evidence of enlargement of the sella turcica or other signs of intracranial pressure.* Its exact cause cannot be determined at the present time. Its constant occurrence, however, in the diseases of the pituitary gland, the writers believe, is sufficient reason for the coining of this clinical type, which will aid in stimulating closer observation of hormonic signs and symptoms in every case of persistent recurring headache, *particularly those which are associated with menstrual disturbances.* The location of these headaches is, in the majority of the cases, unilateral, although the same side of the head is not constantly affected. This location varies considerably in different cases, and even in the same case at different times. It is often located at the base of the skull, both anteriorly and posteriorly. Sometimes it is a diffuse intracranial pain which is difficult to localize, not occurring at one point or portion of the head more than at any other. The patient frequently states that it is a pain indescribable both as to location and character. Very commonly the statement is made that it is of such a peculiar nature that it makes the patient feel that he is becoming mentally unbalanced. This is probably for the reason that it is associated with a considerable amount of mental confusion and lack of concentration. For instance, during its presence there is marked loss of correlation of words and sentences, and the frequent lapse of memory. In pituitary epilepsy, which will be described later, it is frequently one of the most common signs of the aura previous to the convulsion. In many cases *it is associated with ocular and gastric symptoms, which complex simulates very closely that of migraine,* and it will be noted in the histories of this series that the so-called *migraine complex* is found to recur frequently in the bilobar types of hypopituitarism. In a comparatively small number of cases, it was connected definitely with *subjective symptoms of the special senses of smell and taste,* which is confirmation of its connection with a secretory lesion of the hypophysis. It is not easily relieved by medication. Position, posture, surroundings, or external influences, such as light or darkness, have no effect upon it. The fact that so many of these cases are associated with constipation has led many patients to believe that it is due to gastro-intestinal conditions. That the headache in this case (IX), as well as the other hormonic signs, *not* relieved by other medication directed toward the thyroid and the ovaries, *was entirely relieved* by pituitary treatment probably proves that *it was due* to the pituitary dyscrasia.

Treatment.—The course of the treatment given in this case, and the results of the medication applied, combined with the detailed discussion upon treatment in the postadolescent bilobar cases, will be given in Section 7.

Subsequent Course and Effect of Treatment.—The patient has been under observation since her discharge from the hospital, June 6, 1917, to the present time (one year). For the first three months she was placed on simple **thyroid medication,** which was begun at a dosage of grain ss (0.03 gram) three times a day, and finally increased to grains i ss (0.1 gram) three times a day. During this interval, the patient lost nearly 20 pounds in weight. Her headaches occurred less frequently, and were not so extremely painful. Her dysmenorrhea was not affected. She continued to be extremely nervous and irritable, and the pulse would frequently go above 100, which was considered evidence of hyperthyroidism, due to the medication. When this extreme nervousness and tachycardia occurred, the treatment would be interrupted for a number of days. After the pulse had returned to normal, or below 80, thyroid medication was again administered, beginning with a small dose, and gradually increasing this dosage until signs of thyroid intoxication occurred. This treatment was continued until the patient arrived at a stationary point, where the weight did not continue to decrease and the headaches, nervousness, emotional attacks, nausea, vomiting, and dysmenorrhea *remained only partially relieved* or improved. At this time **corpus luteum** was added to the thyroid treatment, in the form of grains v (0.3 gram) of corpus luteum given by mouth with thyroid, grain i-i ss (0.06-0.1 gram) after meals, and corpora lutea, minims xvi (1 c.c.) given intramuscularly twice a week. After two months of this treatment, *there was no further improvement* in the condition. Then **anterior lobe pituitary** extract was added to the thyroid treatment, and the corpus luteum, given by mouth and hypodermatically, was stopped. Soon after this **combined thyroid and anterior lobe pituitary treatment** was given, the patient began to note marked changes toward improvement. After a month's treatment of this kind, the patient *had the first painless period in her menstrual life.* The *headaches, nausea, vomiting, nervous disturbances, mental confusion, and irritability have disappeared entirely.* This treatment has been continued during the past six months with remarkable freedom from symptoms and signs present previous to its administration. On account of the severity and frequency of the various symptoms, particularly the headaches, nausea, vomiting, and mental disturbances, the patient was practically incapacitated from work previous to the institution of this treatment; but since the administration of this treatment this inability for her duties has been relieved completely. The following is the comparison of the weight and measurements:

	June 6, 1917	April 25, 1918
Weight	238 pounds	185 pounds
Measurements:		
Bust	46 in. (117 cm.)	42 in. (107 cm.)
Neck	14 " (36 ")	12½ " (32 ")
Waist	38½ " (98 ")	32 " (81 ")
Hips	58½ " (149 ")	44½ " (113 ")
Arm (upper)	14 " (36 ")	12 " (30 ")

A comparison of the above shows that there is a *loss of weight of 53 pounds* and a marked diminution in all circumference measurements. The greatest is that about the hips and abdomen, which have *decreased fourteen inches* in circumference. At the last observation, on May 26, 1918, the following notes were taken: "Greatly improved, periods regular, of four days' duration, normal amount of flow, absolutely painless for past six months; complete absence of headaches, nausea, vomiting, nervousness, mental confusion, etc." The present medication is thyroid gland grains i ss three times a day, and anterior lobe pituitary extract 1 c.c. hypodermatically every seven days.

Prognosis.—The prognosis in this individual case is undoubtedly very favorable. The fact (1) that there is no neoplastic involvement of the pituitary gland to date, and (2) that the deficiency of the hypophysis, as well as that of the thyroid, can be thoroughly controlled by simple medication, as has been proven by the results of the past six months' treatment, forms a basis for this encouraging prognosis. Whether this patient will recover entirely, or later develop neoplastic changes in the gland, is difficult to foretell. The writers' experience with other similar cases which have been under observation as long as six, eight, and ten years, leads them to believe, however, that the latter is not likely. Whether the function of the thyroid or the pituitary will ever return to normal is also a question. It is more than likely that the patient will require substitution of both these glandular secretions for an indefinite period of time. There is a possibility of reducing the dosage of both the thyroid and the pituitary substances as the improvement continues; and possibly, after a considerable length of time, the patient will be able to have a normal internal secretory balance with the aid of only a small amount of thyroid and anterior pituitary gland taken by mouth.

Pathology.—The pathogenesis of these headaches of pituitary origin, if such a cause can be accepted at all in those secretory diseases of the pituitary gland without enlargement of the sella turcica or other intracranial pressure symptoms, is necessarily in great doubt at the present time. Cushing has attributed them to *distention of the capsule of the pituitary gland,* and we quote verbatim from his description, as follows:

"These headaches, usually bitemporal, often severe and persistent when there is considerable glandular hypertrophy, are presumably due to the distention of the glandular envelope. Our operative experience with Cases XXVI * and XXXVI * would seem to point conclusively in this direction, for the subjective discomforts were immediately relieved in each case by splitting the tense capsule of the gland, which was only moderately enlarged. This suggests that distention of the pituitary capsule is a not infrequent cause of some of the common periodic cephalalgias of obscure origin.

"The pituitary headaches are quite different in type from those incited by a general increase of intracranial tension such as occurs when the hyperplastic gland has burst through its envelopes and extended widely into the cranial chamber (*e. g.* Cases II * and V *). Under these latter circumstances one may expect to find some measure of choked disk superimposed on the primary optic atrophy.

"It is notable that the pituitary headaches proper often subside, coincident, presumably, with a stationary process or with a full distention of the dural capsule and widening of the sella. It is remarkable, however, that the fossa can become greatly enlarged by slow pressure distortion with but a minimum of discomfort (*e. g.* Case XVII *) even at the outset.

"A few of the patients have suffered from cephalalgia of less clear origin. In one acromegalic in particular (Case XXX *) severe racking headaches occur only when he is in an upright position and subside promptly with recumbency. Possibly the abnormally low blood-pressure may play some rôle in this, the discomforts resembling those which follow lumbar puncture with withdrawal of large amounts of fluid."

The pathology in this case (IX) relative to the pituitary gland itself cannot be given. There was probably a colloid adenomatous growth of the right lobe of the thyroid which aided the production of the insufficiency of this gland. It is the writers' opinion that there was an enlargement of the thymus gland, which aids to produce the so-called typical thyroid heart; and while there was no evidence of substernal pressure, a slight amount of dyspnea was present on exertion. The fact that there was a distinct systolic murmur over the pulmonic area, which was projected up toward the left clavicle, and that this murmur disappeared entirely on deep inspiration, when the sternum and thymus were lifted away from the left pulmonary artery, leads the writers to suspect that the thymus was actually enlarged. The relative increase of lymphocytes found in the blood also points to a very slight extent to lymphatism, in which the thymus is usually more or less hypertrophied. Whether the murmurs present with the thyroid heart are due to an enlarged thymus pressing upon the left pulmonary artery, is a debatable question. These is no evidence of any retrogressive change in either the uterus or the ovaries in this case, as is evidenced by the physical examination or by the function or the secondary sexual characters due to these organs. While there were some clinical manifestations of a renal lesion, *the fact that all of these manifestations were removed by thyroid therapy proves conclusively that the kidneys themselves were not decidedly diseased.* The ordinary pathology due to fat infiltration and deposit throughout the skin and the mesentery, previously described, and possibly in the viscera, was present in this case.

---

* Cushing's cases, not the writers' (Engelbach and Tierney).

SECTION 7

PITUITARISM WITH MARKED ABDOMINAL PAIN

(*Bilobar Insufficiency of the Postadolescent, Aneoplastic Type*)

This section will be devoted to a description of 3 cases of hypopituitarism having for their presenting and most distressing symptom a *severe abdominal pain located in the right iliac region.* These cases (X, XI, and XII) have been selected because all 3, after prolonged observation and careful study by competent clinicians, were diagnosed as cases of appendicitis and operated upon for this disease. In none of these cases were the symptoms relieved. On the contrary, in all 3, following these operations, they were much exaggerated. In 2 cases (X and XI) the right ovary and the appendix were removed. In one of these cases the ovary, on histological examination, was found to have a marked decrease in the amount of both graafian follicle tissue and stroma. Following the original operation, this case (X) was reoperated upon, with the consequence of increased production of abdominal pain. In Case XI the abdominal pain, which after the operation was becoming more and more intense, was almost completely relieved by anterior lobe extract therapy. Case XIII is inserted in this chapter merely to illustrate and facilitate the discussion of the hormonic signs pertaining to the bilobar type of pituitary insufficiency occurring during adolescence (*adolescent hypopituitarism*).

Etiology.—The past history of Case X shows that the patient suffered from measles, mumps, and very severe scarlet fever, complicated by nephritis. These occurred during her childhood age, but may have had some effect upon disturbing the secretions of the anterior lobe, which was probably insufficient in her early life. Mumps is a disease which has been frequently found associated with ductless gland dyscrasia. Its direct relation to disease of the gonads has been known for a long time, both orchitis and ovaritis being common complications. This patient also gives a history of a severe fall while she was roller-skating, just previous to the onset of the disorder of the posterior lobe of the hypophysis. It has already been noted in the cases herewith reported, and in the literature, that trauma is a predisposing cause of posterior lobe hypopituitarism. Careful analysis of many cases will demonstrate the relationship of trauma in a higher percentage to disturbances of the posterior lobe than to those of the anterior lobe. The past history in Case XI gives measles, malaria, and small-pox as childhood diseases. The severe abdominal pain in this case did not occur, however, until after the birth of the patient's only child. She dates all of her disturbances from this pregnancy. It is well known that pregnancy, the menopause, and maturity have been definitely associated with the onset of such a large number of pituitary diseases as to place these changes among the etiological factors of diseases of this gland. Many authorities have noted the onset of acromegalia during pregnancy. Other observers have noted the acromegalic changes present during the time of pregnancy, which afterward apparently disappeared entirely. Erdheim and Stumme have demonstrated the enlargement of the hypophysis in pregnant women, as shown by the control autopsy report in these women who die during pregnancy. This case also gave a three-plus Wassermann reaction, which is another factor having considerable influence upon the pituitary secretions. The past history in Case XII gives measles, diphtheria, and whooping-cough as childhood diseases, and *typhoid fever at the age of fourteen.* This typhoid infection occurred just previous to her maturity. As has been stated, typhoid has an etiological relationship to diseases of the pituitary in some cases. There is no definite evidence in this case that the obesity due to posterior pituitary insufficiency occurred immediately after her typhoid. Her menstrual disturbance is such that she must have had some deficiency of the pituitary at this age or previous to it. One would suspect, from the undergrowth of the long bones and the retention of the miniature hands and feet, that this anterior lobe insufficiency had been present at least for a number of years previous to her adolescence.

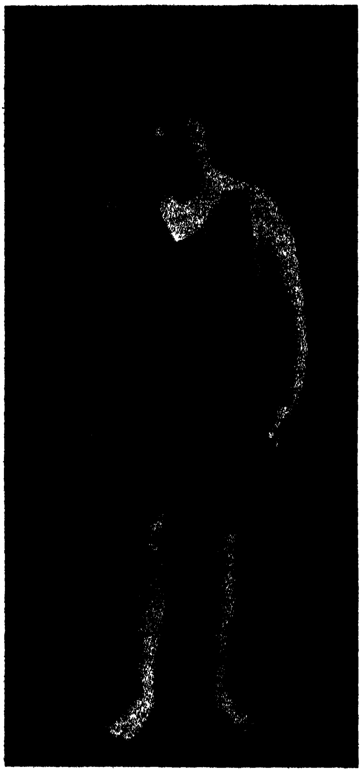
Symptomatology.—HISTORY: Case X.—Miss A. S., aged thirty-one, St. John's Hospital, General No. 2369, April 28, 1917.

Present.—Chief Complaints: (1) *Severe abdominal pain in the lower right abdomen.* (2) *Nausea and vomiting.* (3) *Headaches,* not definitely associated with nausea and vomiting. (4) *Obesity.* (5) *Menses scanty, but regular.*

Duration.—Twelve years.

Course.—(*a*) *Onset:* Gradual. At the age of twenty, following a fall while roller-skating—the patient striking the end of the sacrum—pain was noted in the lower right side, extending through to the right lower lumbar region. Previous to this time the patient had had no dysmenorrheal pains preceding or during periods.

(*b*) *Progress.*—Following this date, menstrual disturbances occurred, consisting of marked pain during the menses and the premenstrual week. This pain in the right lower abdomen, projected through to the back, has been present during the entire course of the disease to the present time. To this has been added, for three or four years, nausea and vomiting and attacks of severe headache. The nausea and headaches were present to the time of the first operation (appendectomy). Previous to this the patient had consulted a gynecologist, who gave her a year's local treatment, consisting of tampons and other applications, without relief of the pain in the right iliac region. Following this time treatment directed towards the colon and the pituitary insufficiency was given. Previous to this there had been some mucous colitis, shown by the passage of more or less mucus, particularly after the periods. Tincture belladonna enemata for spasticity of the colon, and injections of anterior pituitary substance, combined with entire pituitary gland preparation, were given during this time, without very decided effect. The patient became dissatisfied with the results, and consulted a surgeon, who diagnosed her condition as appendicitis, and she was operated upon for this disease. During this operation the appendix and the right ovary were removed. Following this operation the pain in the right side still persisted. Soon afterward the pain began to appear in the left side, and following this there was an interval of three years in which the pain was located first on one side, then on the other, frequently extending across the abdomen anteriorly, but more marked over the old operation scar. The patient had had frequent attacks of nausea, but they have occurred but rarely during the late course of this condition. The so-called nervous headaches are also much less frequent than formerly. For three years following this operation,



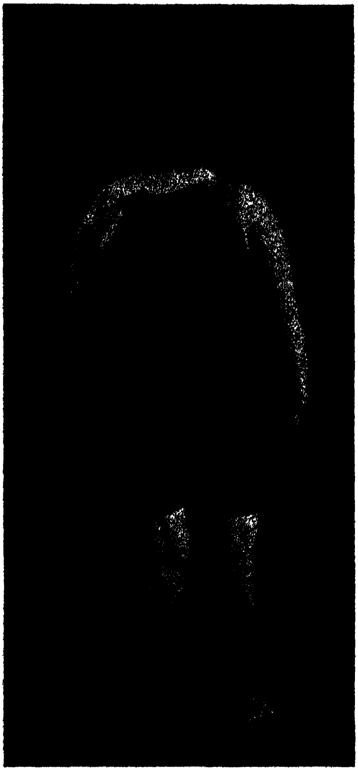
CASE X. FIG. 1.—NOTE SMALLNESS OF STATURE, OSSEOUS UNDERDEVELOPMENT, TYPICAL GIRDLE OBESITY, AND SMALL HANDS AND FEET.

CASE X. FIG. 2.—LATERAL VIEW.

the patient was given treatment consisting of both lobes of the pituitary body, corpus luteum, and thyroid gland. Treatment was frequently interrupted by long intervals during which there was no medicine taken. At this time, on account of the severity of pain and the fact that she had not been relieved by treatment, the patient entered St. John's Hospital for reëxamination. At this examination no new developments relative to abdominal lesions were discovered. There was slight spasticity of the colon, which had been present at previous examinations. The patient insisted upon operation, and an exploratory laparotomy was done, at which time there were found only a very few adhesions around the cecum.

Following this second operation, there was no decided relief from pain. This continued to recur about one week *following* periods. These pains are so intense as to make the patient feel "sick all over." She has, however, not been incapacitated for work. These pains are occasionally associated with gastric disturbances and headaches, but not constantly. The headaches during these attacks are not typical migraine, being disassociated from disturbances of vision, nausea, or vomiting. There has been no history of other conditions, except hemorrhoids, which were operated upon under local anesthesia. There has been pain going down the entire right limb, particularly the lateral aspect, extending from the hip to the foot, very tender to palpation.

The adiposity has no definite onset. Her mother states that she was obese as a baby and in childhood, and has been constantly so more or less to the present time. During the entire course there has been no rapid gain or loss of weight. Skeletal growth has been unchanged since the age of sixteen (no increase in height since that age). No changes occurred in the shape or size of the hands, feet, or face. The weight at the present time is 157 pounds. The periods began at the age of twelve, and were of four or five days' duration to the age of twenty, since which time they have been of three days' duration. The amount of flow was fairly profuse to this age, but since that time has been rather scanty, requiring not more than two pads a day. The individual periods vary in amount, usually every other period being greater in amount than the alternating ones. Following the age of twenty-six or twenty-seven, the patient began to have some pain low in the right side accompanying the periods, not so severe or prolonged, and not covering so wide a distribution, as the pains described above following the age of twenty. At various times during the course the patient has consulted oculists for pains just above the nasal prominence. A number of oculists have examined the eyes and have all reported the findings to be negative, except for a slight hyperopia. The only symptom referable to the thorax is the pain in the mid-portion of the back, between the scapulæ. No subjective dyspnea or other complaints of the chest are present. The patient has abdominal disturbances—feeling of fullness, distention, and very sudden ballooning, occurring as frequently as once a month, especially before menstrual periods, described by the patient as sensation of extreme nervousness and of bloating in the abdomen, not accompanied by fullness or sensation of enlargement of the hands or feet. During this time the patient has very decided emotional attacks, which simulate mild brain storms. There is decided bladder irritation previous to and during the periods, when the patient is forced to empty the bladder frequently. Constipation, which was present to a year ago, has been relieved almost entirely, the bowels at the present time moving, on an average, twice daily. There is constant complaint of backache over the region of the sacrum.

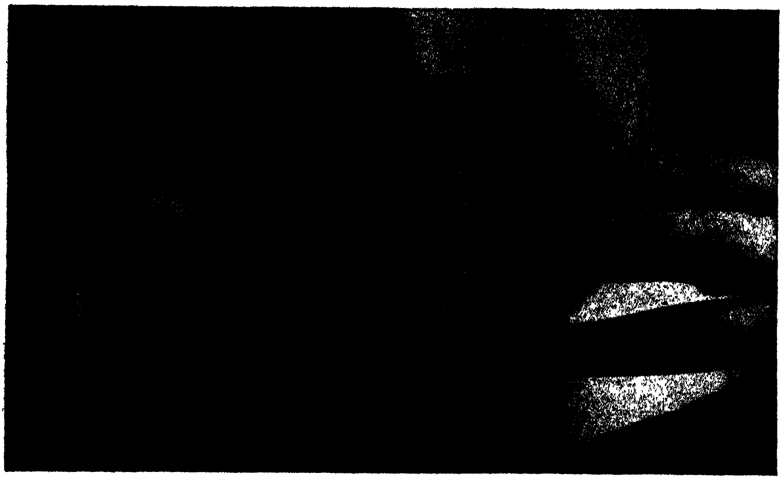


CASE X. FIG. 3.—POSTERIOR VIEW, ACCENTUATING GIRDLE OBESITY.

Past.—Measles, scarlet fever (severe attack in childhood, followed by symptoms supposed to have been due to kidney disease), mumps. Has had aching stiffness in the muscles and joints. Two operations, as noted above, at the age of twenty-six for appendicitis, at the age of twenty-nine for postoperative adhesions, neither affording relief of symptoms.

Personal.—Menstrual history as given under the course of the disease. Drinks five or six cups of coffee daily; six cups of tea. Habits regular, eats but little, is not particularly fond of sweets, candies, creams, etc.

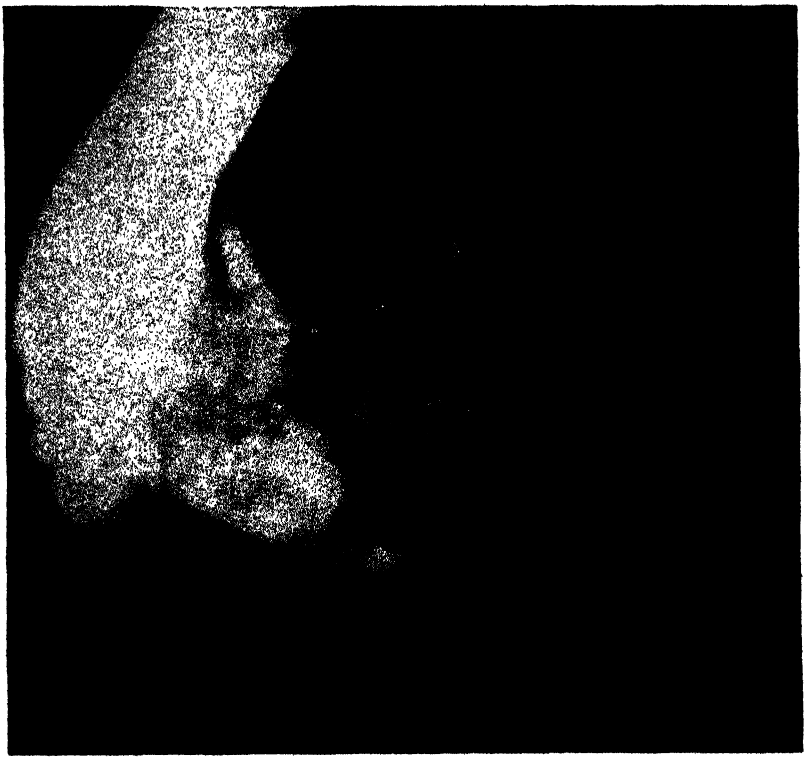
Family.—Mother and father were both short in stature. Mother had considerable obesity, hands and feet were small. Father was man of short stature, without much obesity. One brother, aged thirty, weighing less than 100 pounds, 5 feet 6 inches in height. One sister, aged twenty-seven, of very much the same type as the patient, slightly taller, but with the same characteristic mammary and girdle obesity; hands and feet comparatively small, although larger than those of the patient. One other member of the family died in childhood.



CASE X. FIG. 4.—NOTE GIRLISH TYPE OF FACE, SHORT AND TAPERING FINGERS, SLIGHT SEPARATION OF UPPER CENTRAL INCISORS, AND SMALL LATERAL INCISORS AND CANINES.

EXAMINATION.—*General.*—*Short, very obese girl, with long bone undevelopment. Hands and feet very small* (size of shoe, No. 4½, of glove, No. 6). *Typical pituitary head,* well proportioned to the remainder of the body, classical nose and chin. Very slight *separation of the upper teeth.* No distinct pigmentation about the forehead or angles of the jaw, or other portions of the body. No abnormal distribution of hair; very slight amount, very short, over the manubrium and extremities. No skin lesions or scars, except incision scar in the midline of the abdomen extending from the symphysis to the navel. Very *marked accumulation of adipose tissue in the girdle region,* extending from the navel to the junction of the middle and lower thirds of the thigh; dilated venules over this region. *Breasts large, pendulous,* made up of adipose tissue, without a large amount of glandular tissue. No fat pads about the lateral aspects of the chest or the upper portion, anteriorly or posteriorly. *Pulse, slow,* regular, equal, symmetrical, low volume and tension. Temperament psychoneurotic. *Temperature, 98.2° F.* (36.7° C.) Measurements: From vertex of head to feet, 5 feet 2 inches (157 cm.); circumference of head, 21 inches (53 cm.); neck, 12 inches (30 cm.); chest, at mammæ, 42 inches (106 cm.); waist, 34 inches (86 cm.); hips 45 inches (114 cm.); humerus, 12 inches (30 cm.); femur, 18 inches (46 cm.).

Regional (Positive Physical Signs).—*Head:* Hairline high, even, with no marked encroachment except over the temporal regions. Pain over both posterior occipital nerve exits. *Face:* Small, girlish in type. *Eyes:* Lids slightly puffy, eyeballs somewhat prominent. *Mouth:* Upper teeth slightly separated, small; lower toothline very straight. *Chest:* Considerable tenderness in the lower portion, both sides; thickening of the covering of the lower chest, no fat pads about the axillæ or supraclavicular spaces. *Abdomen:* Marked girdle obesity, in the lower portion of the abdomen; extreme tenderness over the right lower portion particularly, located over a small area in the abdominal wall, seemingly at the right border of the rectus muscle. Accumulation of hard glandular substance in the fat, above the border of the rectus muscle, not superficial; slight rigidity over this painful area. Visceral examination negative. *Vaginal:* Uterus small, infantile; tenderness in the



CASE X. FIG. 5.—NOTE SMALL SELLA TURCICA.

left fornix, none in the right. *Nervous system:* Reflexes exaggerated, no pathological ones.

Laboratory Findings.—*Urine.*—Single specimen, pale, specific gravity 1.022, reaction acid. Trace albumin. Dextrose, casts, leukocytes, and erythrocytes negative.

Feces.—Following blood-free diet, brown, formed. Mucus, pus, ova, parasites, and occult blood negative.

Blood:

Erythrocytes	4,448,000
Leukocytes	10,000
Hemoglobin	92 per cent.
Stained smear	normal
Wassermann	negative

Stomach Content:

Ewald test meal, one hour in stomach, liquid, no food sediment. Free hydrochloric acid 60, total acidity 80, small amount of mucus. Lactic acid and microscopic examination negative.

Chemical Blood:

Blood sugar	0.064 per cent.

Special Examinations.—*Roentgenogram of Head.—Sella turcica small.* Other markings normal.

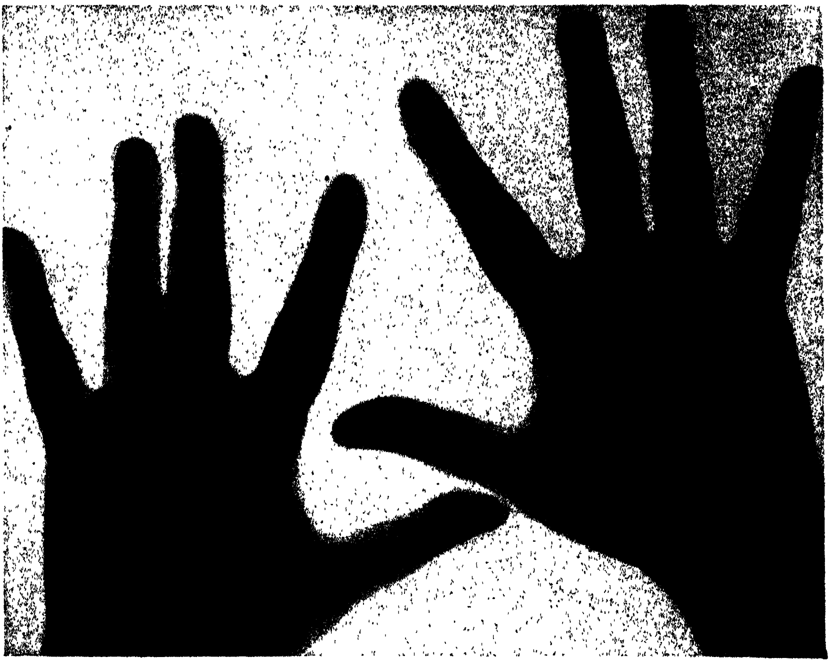
Roentgenogram of Hand.—Metacarpal and phalangeal bones long and slender, absence of tuberosital markings in the terminal phalanges.

History: Case XI.—Mrs. R. B., aged twenty-eight, General No. 1294, St. John's Hospital, February 26, 1918.

Present.—Chief Complaints: (1) *Severe pain in the right iliac region,* present previous to and increased following right ovariectomy. (2) Constant *dull pain in the small of the back,* increased on movement of the spine. (3) *Menstrual disturbance;* periods regular, but flow slight, lasting two days. (4) *Extreme nervousness* during the two weeks *previous to the periods.* (5) *Gas pains* and sudden attacks of *abdominal distention.* (6) Painful attacks of *bladder irritation* previous to the periods. (7) *Transient enlargement of the hands, feet, and face,* associated with *localized perspiration* of these parts. (8) *Dryness and harshness of the skin.* (9) *Tenderness of the scalp,* "pulling sensation" of the hair. (10) *Yellowish pigmentation,* occurring in the form of *large blotches about the face and neck.* This becomes more intense with attacks of enlargement and puffiness of the face.

Duration: The condition has lasted for ten years.

Course.—(*a*) *Onset:* This was sudden, coming on as pain in the right lower quadrant of the abdomen, following childbirth, this pain occurring one week previous to the periods. The delivery was apparently normal, non-instrumental, and free from infection. Following this, however, there continued for six or seven weeks a profuse lochia. This then ceased for two or three weeks, when the flow again started. The menses were very slight, the flow lasting two or three days, occurring every three weeks. This continued until five years ago, when the patient consulted a gynecologist, who performed a curettement, which was followed by restoration to normal of the intervals between the periods, the character of the flow remaining as previous to delivery. The patient remained under observation of a gynecologist for one year because of the scanty periods and pains occurring in right iliac region previous to the flow, which were thought at first to be due to adnexal disease. After one year's observation, and persistent local and general treatment, without relief of this pain, the gynecologist finally concluded that *it was due to chronic appendicitis,* and recommended an operation. The patient did not accept this operation. Instead, she consulted a surgeon, who, after a few months of observation, confirmed the previous diagnosis of appendicitis and performed an operation.



CASE X. FIG. 6.—NOTE LONG, SLENDER METACARPAL AND PHALANGEAL BONES, DECREASED DENSITY, AND SLENDER CHARACTER OF UNGUINAL PHALANGES, WITHOUT TUFTING.

(*b*) *Progress:* At this operation the *appendix* and *right ovary were removed.* Following this operation, the patient continued to have this pain, which not only became more intense, but was present during two instead of one week preceding menstruation. Later it also occupied the left side of the pelvis, and was frequently present in both sides at the same time. The remaining two weeks of the menstrual month were usually comparatively free from abdominal disturbance for a number of years. During the past year and one-half, however, more or less constant pain has been present in the right side, becoming very much aggravated and frequently accompanied by pain on the left side two weeks before the beginning of the flow. Soon after operation the abdominal pain was accompanied by severe pain in the lumbar region, which gradually increased in intensity and duration with the progress of pain in the abdomen. The periods began at the age of thirteen, and from the onset were very scanty in amount (requiring not more than one pad), slight flow for the first two days, with very faint trace on the third, of two or three days' duration. Intervals were regular until the time of childbirth, since which time the periods have been as described above. The time of onset of the other chief complaints cannot be determined absolutely; but the patient dates all of them from about the age of maturity. The extreme nervousness consists of marked irritability, tremor, insomnia, and restlessness, occurring usually in the first or second premenstrual week, at times following excitement or overexertion. During these weeks the patient develops severe "nervous chills," lasting for ten or fifteen minutes, and at times other contractures and convulsions (which were considered hysterical). The gas pains and sudden attacks of abdominal distention have occurred between the periods, and frequently independent of menstrual disturbances. They have been more severe and have occurred more frequently, however, during the time of the other premenstrual symptoms. The patient first noticed *sudden enlargement and puffiness of the hands, feet, and face* following the birth of her child ten years ago, *associated with marked chloasmic discoloration of the face and neck.* This pigmentation, as well as the swelling and puffiness, disappears soon after the period, and is usually absent for two weeks, recurring with the next period. The bladder irritation symptoms are also definitely associated with the premenstrual week. Changes in the dermal system, consisting of dryness and harshness of the skin, tenderness of the scalp, and "pulling sensation" of the hair, have been noticed only during the last two or three years, not associated particularly with the periods, but present more or less constantly. The patient has not gained weight rapidly, but there has been a gradual increase from 140 to 205 pounds. At times there has been very marked *somnolence,* the patient finding it difficult to keep awake *in the daytime,* even while talking, and this is associated with *insomnia during the night,* due to nervousness and restlessness. No signs or symptoms referable to other systems.

Past.—Measles, malaria, probably small-pox. Operations as noted above. No injuries.

Personal.—Has one child, ten years old. No other pregnancies. Appetite good. Bowels regular. Disturbance of urination as noted. Sleeps well except immediately before the period. Tea and coffee moderately; no alcohol.

Family.—No family history of hereditary diseases.

EXAMINATION.—*General.*—*Obese woman, weight, 205 pounds,* obesity not particularly limited, but *marked about the girdle. Mammæ extremely large,* containing considerable amount of mammary tissue. Fat folds present along the posterior and lateral portions of the chest. No marked demarcation of obesity at the wrists or ankles. Decided *chloasma pigment about the forehead, eyelids, and face.* No abnormal distribution of hair. *Pulse, slow,* regular, full, equal, symmetrical, slightly increased in volume and tension, rhythm good. Temperament psychoneurotic, well controlled. Skin rough, palms moist. *Temperature, 97.4°-98.6° F.* (36.3°-37° C.); *pulse, 72-82;* respiration, 20-22.

Regional (Positive Physical Signs).—*Head:* Large; anterior-posterior diameter increased. *Eyes:* Marked chloasma about the lids. *Face:* Hexagonal, features coarsened. *Nose:* Large, blunted, full. Rounded superior maxillary prominences. *Chin:* Wide, rounded. *Mouth:* Lips full; upper incisors widely separated. *Neck:* Thyroid gland slightly enlarged, both lobes, not vascular or pulsating. *Chest and abdomen,* visceral examination negative. *Vaginal:* Uterus large, anterior position; cervix slightly irregular, no masses in fornices, left ovary not palpable. *Extremities:* Slight abnormal distribution of hair over the lower. *Hands* of typical acromegalic type, wrists very wide, fingers wide, rounded, ends plump; nails comparatively small, white crescents not showing. *Feet* large, arches high, toes very large, rounded.

LABORATORY FINDINGS.—*Urine.*—Single specimen, color straw, reaction acid, specific gravity 1.010. Dextrose, leukocytes, erythrocytes, and casts negative. Trace of albumin.

Feces.—Brown, formed, trace of occult blood. Mucus, pus, ova, parasites, negative.

Blood:

Erythrocytes	5,460,000
Leukocytes	5,800
Hemoglobin	93 per cent.
Stained smear	normal
Wassermann	positive, three-plus (Wassermann of husband, negative)

Blood-sugar:

First specimen	0.090 per cent.
Second specimen (following 500 grams (18 ounces) dextrose by mouth in twenty-four hours, and adrenalin (1/1000) m. x. 'H')	0.076 " "

SPECIAL FINDINGS.—*Fluoroscopic.*—*Head, chest, stomach,* negative.

Trochoscopic.—Marked redundancy of the pelvic and of the iliac colon.

Roentgenogram of Head.—*Sella turcica small.* No other abnormal markings.

Atropin Test: Negative.

HISTORY: CASE XII.—Miss S. D., aged twenty-eight, single, General No. 569, St. John's Hospital, November 27, 1916.

Present.—Chief Complaints: (1) *Dull, aching, drawing pain in the right hypochondrium,* slightly above and about three fingerbreadths to right of the umbilicus. Tenderness in this area, no radiation. (2) *Chronic constipation.* (3) *Sense of fullness one-half hour after meals,* accompanied by eructations, some intensification of abdominal pain, occasional nausea and vomiting, with relief. (4) On four or five occasions there has been a *severe attack of epigastric pain,* accompanied by repeated vomiting, with relief. No temperature, no distinct history of colic requiring hypodermic. All symptoms aggravated during the menstrual period. (5) *Some increased nervous irritability.*

Duration.—Ten years.

Course.—(*a*) *Onset:* Sudden. Without any known exciting cause, the patient suddenly became nauseated, followed by persistent vomiting for about ten hours. Vomitus contained a considerable amount of mucus. This attack was unaccompanied by severe pain, jaundice, headache, or eye disturbances. No diminished or increased urinary output. Following this first attack the patient had more or less constant indigestion, feeling of epigastric distention, fullness, belching, pyrosis, acid eructation, and occasional nausea and vomiting, with relief of symptoms. During these attacks there was some increase in severity of the hypochondrial pain and tenderness. Pain and tenderness not relieved by vomiting or bowel movement.

(*b*) *Progress.*—This course persisted for eight years without much modification, with more or less constant hypochondrial pain and epigastric distress after meals. Occasional vomiting, with relief. Chronic constipation persisted throughout this period, but satisfactory bowel movements produced modification of symptoms. No mucus noted in the stools. At no time in these eight years has there been distinct colic, jaundice, temperature, or concomitant symptoms of infection. There have been short periods of relief, from a few days to a week. The symptoms have always been increased during the menstrual periods. The periods, however, are regular, but painful. No migraine history. Two years ago the *condition was diagnosed chronic appendicitis,* and an *appendectomy was done.* Since operation there has been modification of the epigastric symptoms, but the hypochondriac pains have been unchanged: Distention, pyrosis, eructations, etc., are less severe, but still present, occasionally accompanied by vomiting, with relief. Lying on the left side moderates the pain; no nocturnal distress. Most marked relief has been found in relief of the constipation. No signs or symptoms referable to other systems.

Past.—Measles, diphtheria, whooping cough, *typhoid fever* at the age of fourteen (of nine weeks' duration), without complication.

Personal.—Coffee moderately; alcohol in moderation. Appetite good. Insomnia in the early portion of the night. Chronic constipation, as mentioned. Intolerance for carbohydrates and fats. Menses began at the age of fourteen, always regular, *scanty, lasting two days, requir-*

ing two pads during the entire period, *very painful*, accompanied by symptoms referred to under the present history.

Family.—Father dead, aged sixty-eight, senility. Mother dead, aged fifty-nine, pneumonia. Four sisters living, well. One sister died of cardiac disease, secondary to rheumatism. One brother living, well. No family history of liver or kidney trouble, tuberculosis, cancer, nervous diseases, sick headaches, or goiter.

EXAMINATION.—*General.*—*Height, 5 feet 2 inches* (156 cm.); *weight, 142 pounds.* Development, *stocky, with girdle obesity. Hands short, broad* (size of glove, No. 5¾), slight fullness of dorsa and of backs of fingers. Arms plump, plumpness stopping more or less abruptly at the wrists. *Feet small,* of the same type as the hands (family characteristic). Distance between the styloid process of the radius and the olecranon is short. Color good, nails pink, lips pink, with very cyanotic tinge. Pulse, slow, regular, of no particular character, normal volume and tension, equal, symmetrical. No abnormality of gait or station. *General hyperesthesia to pressure,* superficial tenderness of the skin, tendency to easy bruising. Temperament psychoneurotic.

Regional (Positive Physical Signs).—*Head:* Small, face full, rounded, with fat padding beneath the jaw. *Mouth:* Lips full; teeth considerably decayed. *Neck:* Thyroid not enlarged. *Chest:* Visceral examinations negative. *Abdomen,* negative. *Vaginal:* Uterus very small, retroverted; tubes and ovaries not palpable. *Extremities:* Long bones short, hands and feet small, typical hypopituitary hand. Dilated venules on external portions of thighs.

LABORATORY FINDINGS.—*Urine.*—(*a*) Single specimen, pale, reaction acid. Dextrose, albumin, casts, leukocytes, and erythrocytes negative.

(*b*) Twenty-four-hour specimen, 1,600 c.c., cloudy, reaction acid, specific gravity 1.006. Dextrose, leukocytes, erythrocytes, and casts negative. Trace of albumin, epithelial cells present.

Feces.—Following blood-free diet, white, formed. Mucus, pus, ova, parasites, and occult blood negative.

Blood:

Erythrocytes	4,900,000
Leukocytes	8,400
Hemoglobin	89 per cent.
Stained smear	normal
Wassermann	negative

SPECIAL EXAMINATIONS.—*Fluoroscopic.*—*Head, chest, stomach,* negative.

Trochoscopic.—Marked spasticity of descending, iliac, and pelvic colon.

Roentgenogram of Head.—Sella turcica normal. No abnormal markings.

Diagnosis.—The diagnosis in these 3 cases is hypopituitarism of bilobar involvement, postadolescent variety, aneoplastic type.

This diagnosis is based upon the signs of insufficiency of both lobes of the pituitary gland. Cases X and XII occurred earlier in life than Case XI; but all are probably better classified with the postadolescent variety than as pre-adolescent or the so-called adolescent type as described by some authors. It is unnecessary to go into the analysis of the hormonic signs of each lobe in these cases. The anterior lobe insufficiency is undoubtedly proved in all of the 3 cases by the arrested skeletal growth, or the marked change in the flat, short, and acral bones at the age of maturity, and the very marked abnormal menses from the very first period. The evidence pointing toward the insufficiency of the posterior gland consists of classical obesity, combined in the 2 cases (X and XI) with decreased metabolic changes, and with a slow pulse and subnormal temperature in all 3 cases.

The *most conspicuous complaint present* in all of the 3 cases *is the extreme amount of abdominal pain located in the right iliac region.* This was so severe and persistent in all these cases, that *each case was finally operated upon, under the diagnosis of appendicitis.* In 2 of the cases the right ovary was removed, which would incline one to believe that there were no marked changes in the appendix. In one of the cases the appendix and the ovary were examined after operation and found to be negative for inflammatory and other abnormal histological changes. The ovary in this case shows some decrease, but not complete aplasia of the graafian follicle tissue and stroma. This complete hypoplasia would not be suspected, on account of the history of imperfect, scanty menses present throughout the entire course. There was no control upon the operative diagnosis in the other 2 cases. The fact that each one of these cases had the same pain following operation in a more severe and aggravated form, would incline one to believe that in none of the cases was the appendix the absolute cause for the pain. That this is a very common complaint in many other cases not having appendicitis as a concomitant disease, would further lead one to believe that the diagnoses in these cases were probably erroneous. In 2 of the cases there were marked nausea and vomiting associated with this right-side abdominal pain. In one case (XII) the vomiting was particularly severe, persisting for ten hours during one attack. In two of these cases there was a spastic colitis present at the examination, a number of years following operation. In both of these cases the treatment for spastic colitis, consisting of tincture belladonna oil enemata and tolerant doses of belladonna by mouth, did not relieve the abdominal pain. In one of the cases (X) there was associated with the spastic colitis a mucous colitis. The relief of the spasm of the colon and complete regulation of the bowels did not relieve this patient of the persistent abdominal pain.

A very careful analysis of these abdominal attacks in which the pain was the predominating symptom, proved that they did not have the clinical picture of acute appendicitis. The pain in all three attacks began as a localized pain in the right iliac region. It was never associated with temperature; and never began as a diffuse abdominal pain, localizing later over McBurney's point. In the early course of these cases it was present during the premenstrual or menstrual week. It usually was relieved to a considerable extent following the first two days of the menstrual flow, and during the early course of each case would be absent for at least two weeks following menses. When nausea and vomiting were associated with this pain, the gastric attacks were usually much more prolonged and severe than those acute intermittent attacks of nausea and vomiting associated with appendicitis. It is true that there was a considerable amount of localized pain and tenderness over McBurney's point, and that this sign was present not only previous to the menses, but throughout the entire month. Considerable emphasis and detailed attention has been given to the character of the pain in these 3 cases, merely to prove, first, that it was not due to a complication of appendicitis, and second, to demonstrate the actual difference between the lower right abdominal pain associated with bilobar hypopituitarism and mild chronic appendicitis. These 3 cases were selected because they had all been operated upon for this disease; it is thought that all of them proved rather conclusively that appendicitis was not an accompanying lesion. On the contrary, there is a severe abdominal pain in hypopituitarism frequently located in the lower right side of the abdomen, so closely simulating appendicitis as to be mistaken for this disease, even by the most skillful observers, after having these cases under observation for a considerable length of time. That this diagnosis was not made upon superficial observation is proved by the fact that one case had been under the observation of a competent gynecologist for over a year, and another under the observation of a careful surgeon for three months, before the patient was advised to undergo operation.

The cause of this abdominal pain in these cases is very difficult to explain. It probably has an entirely different cause than the pain that occurs with the overactivity of the posterior lobe of the hypophysis. In those cases (having a hypersecretion of the posterior lobe) the complaint is probably due to overstimulation of the circular muscle-fibers, particularly of the large intestine, producing typical severe intestinal colic. It is well known that the extract from the posterior lobe and infundibulum of the hypophysis has a decided effect in stimulating unstriped muscle-tissue. This is proved very conclusively by the effect of injections of pituitrin (substance of posterior lobe) upon the uterus and upon the intestinal peristalsis. The writers have noted that in giving this substance in the treatment of hyposecretions of this lobe, or in combination with anterior lobe extract in the treatment of bilobar insufficiencies of the hypophysis, the patient complains, usually in from four to seven minutes after the injection of a moderately sized dose, of severe abdominal pain, which is followed within ten to fifteen minutes, in some cases, by bowel evacuation. In these 3 cases, however, there were absolutely no evidences of hypersecretion of this lobe. On the contrary, they all presented definite signs of inactivity of the posterior lobe throughout the entire course. None of them followed or were secondary to overactivity of the posterior lobe of the pituitary. So the cause for pain in these cases must be explained upon the basis of an inactivity of the posterior or the anterior lobe of the hypophysis. The fact that, during the earlier course of all these 3 cases, the pain was present during only the premenstrual week of the month, leads the writers to believe that it is more likely that this pain is due to an insufficiency of the anterior lobe in the hypopituitarisms, instead of being at all related to the posterior lobe. All of these cases were associated with pain during the period, but they differ from the other dysmenorrheas in having pain a week, or, during the later course, two weeks previous to the onset of the flow. In these cases, as well as in the others, the abdominal pain is relieved almost entirely for a week or two following the period. This differs to a very marked extent from the constant abdominal pain produced by the posterior lobe hypersecretions, which has no special relation to the menstrual week. It is impossible to go farther into the pathogenesis of this pain, from the personal experience of the writers, than to state that in one of these cases (XI), as well as in those of other clinical groups, in which it was associated *with marked enlargement of the structures of the face, hands, and feet, the pain, as well as the other symptoms, has been almost completely relieved by giving anterior lobe extract hypodermatically, and substance of anterior lobe by mouth.* In the 2 other cases, one of which (Case XII) was very insufficiently treated, having had only six treatments, there was no appreciable effect from the exhibition of this same treatment of one injection a week.

It will be noted that the other chief complaints in these 3 cases were confined to a large extent to the abdominal disturbances. Two of these cases have had some of the constitutional disturbances which are present in the postadolescent bilobar hypopituitarisms occurring later in life, such as syncopal attacks, headaches, and extreme nervous irritability, associated directly with the periods. These constitutional disturbances occur during the premenstrual week at the time that the abdominal pain is at its height. It will also be noted that later in the course of all 3 cases, this pain was not limited to the right side of the abdomen, but that in all 3 there was a definite history of pain occurring in the left side, sometimes being present across the entire lower abdomen, described as a deep-seated pelvic pain. In one case (X), following the second operation, this pain has become almost continuous during many months of the year, remitting during an occasional month, only during the first or second week after the period. In this case it became more severe following each operation, and was not relieved by three *x*-ray exposures given for sterilization of the remaining ovary, combined with pituitary and ovarian therapy. The fact that the pain did become more severe in 2 of the cases in which the right ovary was removed, might be additional proof that it was due to a certain extent to insufficiency of the ovary, from lack of anterior lobe secretions. In the other case, in which only the appendix was removed, the pain was apparently not intensified, although it continued to be present at the same time and with about the same severity.

The histological examination of the ovary which was removed in Case X at first operation, demonstrated the decreased amount of interstitial tissue of this organ, without a complete absence or aplasia of this substance. This is taken as further proof of the deficiency of secretion from the anterior lobe of the pituitary. Cushing found in a number of cases of hypopituitarism in which he removed a portion of the testicle during operation upon the pituitary, that this same paucity of the interstitial cells of Leydig of the testicle was present in these cases in the male. Case X showed also decrease but not absence of the graafian follicle tissue. This will explain why one of these 3 cases (XI) was able to conceive, although she undoubtedly had partial insufficiency of the ovary. One of the reasons for her seeking medical aid was the prolonged sterility which followed the birth of her first and only child. Neither of the other patients was married, although both show evidence of lack of sexual characters, and one gives a very frank history of frigidity (Case X).

Complications and Sequelæ.—There are no decided complications or sequelæ in any of these cases referable to other ductless gland, organic, or structural diseases in the body, except that due to such changes as obesity, arrested skeletal growth, etc. In Case X thyroid gland was given for a prolonged time without any effect upon the symptoms or obesity. Case XI is reacting very satisfactorily to the simple pituitary treatment, without addition of other ductless gland preparations. Case XII did not remain under observation long enough to receive treatment of any kind, so in this the effect of treatment as an aid to the diagnosis of other endocrinous glands complicating pituitarism, cannot be stated definitely. Two cases (X and XII) had only very slight or no pigmentation, limited entirely to the face and forehead. This was in the form of localized chloasmic spots, which the writers believe can be due entirely to the anterior lobe of the pituitary. Case XI had a very decided pigmentation about the face, head, and neck, which was transient in character, accompanying the puffiness and swelling of these parts, occurring just previous to the menstrual disturbances. The fact that this pigment was so intermittent in its occurrence, and that it was present so decidedly with other evidences of disturbance of the anterior lobe, and not with any due to the adrenals, indicates its pituitary origin. In this case (XI) the pigment was decidedly increased during the two or three days just before or the first days of the period, and became much less intense four or five days after the period. There was no other evidence of adrenal disturbance, such as lack of vasomotor control or changes in the blood-pressure. The pineal gland, the thymus, and the parathyroid showed no clinical evidence of change in any case.

Associated Diseases.—In Cases XI and XII there has been no definite association or susceptibility to other diseases produced by the hypopituitarism. Case XI gave a positive serological reaction for lues, without any other definite evidence of specific disease. The husband of this patient gave a negative blood reaction for this disease. It has been the contention of some writers (Draper) that these cases of hypopituitarism, when once infected with lues, have a tendency to very early cerebrospinal lesion. This certainly was not the case in this instance. Careful history for acute infection, particularly of the respiratory tract, in these 2 cases was negative. Contrary to this, Case X seems to be especially susceptible to respiratory infection. During the winter months she is almost continuously complaining of rhinitis, bronchitis, or a combination of the two. She seems to have the same susceptibility to these diseases as the later postadolescent cases reported in Section 8, while the other two (XI and XII) were apparently absolutely free from this susceptibility. Marked constipation was a common complaint in all 3 cases, but this was more than likely a sequel or a complication than an associated disease. Spastic colitis was a complication in Cases X and XI, but not in Case XII, in which trochoscopic examination demonstrated an enlarged, atonic colon, with markedly redundant iliac and pelvic colons. Mucous colitis was an additional associated condition in Case X, during the early course of the disease; but this, as well as the spastic constipation, has entirely disappeared during the last year of the course.

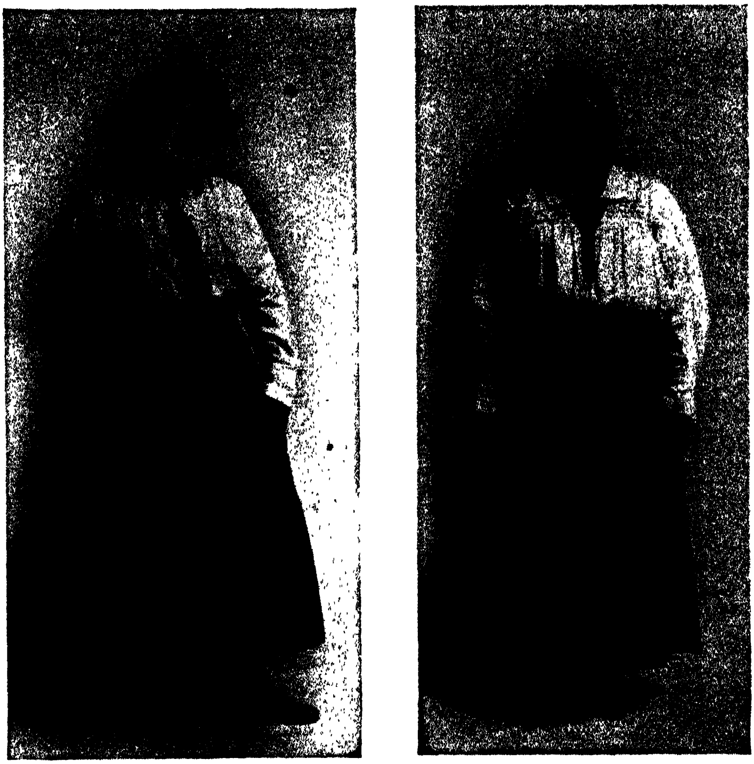
Adolescent Hypopituitarism.—The above and similar cases have been described as *postadolescent types* of hypopituitarism. The writers have one other case under observation (XIII), a summary of which will be described at this place; because, with the exception of the absence of the *marked abdominal pain,* it is very similar to the above reported cases (X and XII) in general stature, obesity, and disturbance of the menses.

History: Case XIII.—Miss J. G. E., aged eighteen, schoolgirl.

Present.—The patient was a well-developed, well-formed child, inclined to be obese in her girlhood days. This obesity gradually increased until, during the time of observation at the age of eighteen, she had reached the weight of 261 pounds. There has been no sudden change from a non-obese to an obese state. The skeletal growth has not been interrupted or retarded for any definite period, at any age. The *first menses occurred at the age of fifteen, was scanty in amount, short in duration, lasting not more than two days,* and free from pain. Since that time her *periods have been irregular, occurring every three to six months,* never lasting more than two days, always very small in amount, not requiring more than two menstrual pads a day. They have been free from pain or constitutional symptoms of any kind. During this time the patient has gradually and progressively taken on an enormous overgrowth of subcutaneous adiposity. This has been confined to a large extent to the girdle region. There has been, however, some universal adiposity. Trauma, infection, or disease of any kind associated with either the onset or the course of the disease, have been absent. There is a tendency to sprain the ankles, probably due to the excessive weight and frail ankle support.

Family.—Father rather typical hyperpituitary type of individual, who later in life has taken on the tendency to hypopituitarism. Mother, from description, was small, infantile type of individual.

EXAMINATION.—*General.*—*Enormously obese young girl, height 5 ft. 5 in., weight 261 pounds,* showing *typical girdle obesity,* associated with general adiposity, involving to a slight extent the arms and legs. No supraclavicular fat pads, no padding on dorsum of hand. No pigment or abnormal distribution of hair, no skin lesions or scars. *Skin very thick, inelastic,* and associated with very dense subdermal pseudo-infiltration. Skin rather dry and harsh, excess of perspiration noted in the armpits and intertriginous surfaces. Marked *folds of fat hanging from the lateral surfaces of the chest and abdomen;* breasts well developed, but not pendulous. *Pulse, very slow,* equal, symmetrical. Temperament phlegmatic.



A B

CASE XIII. FIG. 1, A AND B. (A) *Case X.* (B) *Case XIII.* NOTE EQUALITY IN HEIGHT, PRACTICALLY SAME AMOUNT OF ADIPOSITY (CLASSICALLY DISTRIBUTED), AND SMALL HEAD, HANDS, AND FEET.

Regional (Positive Physical Signs).—*Head:* Very small in comparison with the rest of the body. *Face:* Youthful, rounded, well proportioned, free from chloasma. *Nose:* Straight, clean-cut. *Chin:* Sharp, pointed, not projecting. *Mouth:* Teeth straight, no separation of the upper incisors, lower incisors not overcrowded, no dedentition or loss of teeth. *Neck:* Rather small, thyroid not enlarged, no supraclavicular fat padding. *Hands:* Unusually small as compared with the rest of the body, terminal phalanges of fingers tapering, white crescents of the nails not visible. *Feet: Small. Long bones,* fairly well developed.

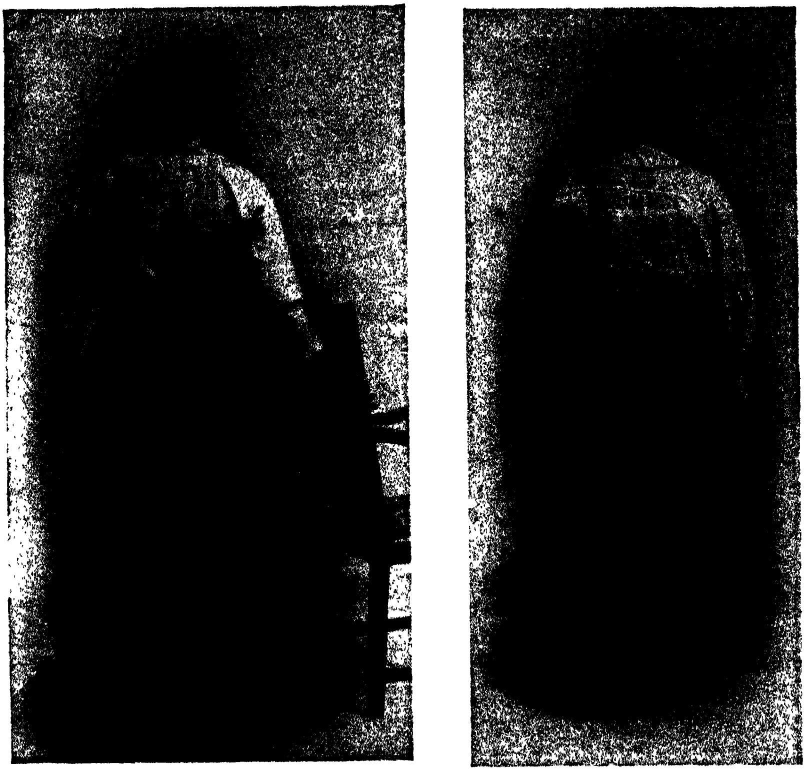
A B

CASE XIII. FIG. 2, A AND B. (A) *Case X.* (B) *Case XIII.* NOTE EQUALITY IN HEIGHT, SIMILARITY OF ADIPOSITY, CLASSICALLY DISTRIBUTED, AND SMALL HEAD, HANDS, AND FEET.

LABORATORY FINDINGS.—*Urine, feces, blood,* negative.

COURSE OF CASE UNDER OBSERVATION.—Treatment consisted of **anterior lobe of pituitary, thyroid gland, and corpus luteum.** The patient's periods returned practically to normal, occurring regularly each month, and lasting three or four days, with occasional excessive menses lasting six or eight days. The thickness of the skin, the inelasticity, and the infiltration of the subdermal tissue have been markedly reduced. The general weight of the patient has not been decidedly affected. There has been a reduction in weight from 261 to 248 pounds in fourteen months' treatment. The treatment in this case has not been continuous or persistent, particularly the hypodermatic medication, although the intermittent treatment, as stated above, has restored the periods to normal and has relieved the patient of many constitutional symptoms.

Case XIII reacted fairly well to simple substitution treatment, whereas Case X obtained no reaction. Both cases, however, were only indifferently treated. Case XIII obtained much more regular treatment, consisting of hypodermics of the substance of both lobes of the pituitary, on an average of every two weeks, and for limited periods of time small doses of thyroid and corpus luteum by mouth. Case XIII had an additional partial hypothyroidism which was not present in Case X.



A B

CASE XIII. FIG. 3, A AND B. (A) *Case X.* (B) *Case XIII.* NOTE EQUALITY IN HEIGHT, SIMILARITY OF ADIPOSITY, CLASSICALLY DISTRIBUTED, AND SMALL HEAD, HANDS, AND FEET.

Adolescent Pituitarism.—The term *adolescent pituitarism,* which has been given to this type of case, adds to the confusing classification to which these diseases have been subjected. This term has been applied for the reason that nearly all of these cases assume practically the same stature and remain in the same obese deformity for a number of years. It serves very well to identify, in a general way, this type of individual. They have insufficiencies of both lobes of the pituitary gland. The insufficiency is one that does not begin just at the age of adolescence, but has its onset years before that time, in order to produce the unusually small head, hands, and feet which characterize the skeletal growth in these cases. The enormous obesity is that which also occurred, in some of the cases, years before adolescent life. It is true that it was not observed or thought significant until possibly a few years after adolescence. This is due to the fact that it is not until this age that the disturbances of the menses are recognized as a possible cause for the obesity; and *this association of menstrual disturbance and obesity, occurring a short time after maturity,* has had a great deal to do with the production of the name of *adolescent* hypopituitarism. This term is not as well designed as that of *adolescent hypothyroidism.* This is due to the constant secretions of the pituitary gland operative during the early years of life, continuing in the normal individual through adolescence, into adult age. This is not true of the thyroid. It is well known that the thyroid activity changes decidedly during maturity, although it is effective long before this age, and continues to be so until after the age of the menopause. Maturity, for this reason, has a more decided effect upon the function of the thyroid than it does upon the pituitary gland, and many more cases are definitely related to the age of maturity than are those of the pituitary gland.

Treatment.—PROPHYLACTIC.—The prophylactic treatment in these cases should be given more consideration, particularly in those individuals who have, previous to maturity, evidence of insufficiency of the pituitary gland, as demonstrated by the hormonic signs of the osseous system, such as retarded growth and small acral parts, and in those having subnormal temperature, a slow pulse, or tendency to opposite sex characters. *Early obesity is the most striking sign which should attract attention as a possible hypophyseal anomaly.* This is especially important in those children whose parents have signs of ductless gland dyscrasia, such as undergrowth of the skeleton, marked obesity, history of diabetes mellitus or insipidus, etc. It is not unlikely that if these cases were observed very carefully for pituitary disturbances early in life and given **glandular treatment,** many might avoid the extreme disfiguration and incapacitation to which untreated cases are doomed.

ACTIVE TREATMENT.—The active treatment in those cases which are not associated with hypophyseal tumors (enlargement of the sella turcica or intracranial pressure symptoms) consists of an attempt **to substitute the secretions of both the anterior and posterior lobes.** In those cases which seem to have a predominance of one lobe over the other, it is well to try, beginning with large doses of that particular lobe, to compensate for this insufficiency alone. If this is not productive of good results, a combination of substances from both lobes should be given. These preparations should be given both by mouth and hypodermatically. The exact size of the dose has not yet been satisfactorily determined, and each case is an individual problem. Both the anterior and the posterior lobe preparations are now on the market in such forms as can be given by oral administration. Extracts of these lobes are also obtainable and they should be used in conjunction with the preparations given by mouth. On account of the non-standardization of these preparations, it is difficult to determine the size of the dose. Probably the best general rule to adopt is that which gives sufficient dosage, by mouth or hypodermatically, to overcome the abnormal hormonic signs and symptoms *without* producing untoward reaction. There is very little danger of producing reaction with the *anterior lobe substance*. This is not true, however, with the extract of the *posterior lobe*. The writers have made it a rule, as stated previously, to measure the dosage by the tolerance of the patient, as determined by the effect of the injections upon the *intestinal peristalsis* and the *general stability* of the patient. A dose which produces severe abdominal cramps and pain, followed in a short time by bowel movement, should be taken as a tolerant one, whereas a dose producing the *general reaction, consisting of marked tremor, pallor, syncopal sensations, and emotional disturbances, is considered too large*. It should also be borne in mind that a great majority of these cases of considerable duration become polyglandular diseases, *i. e.*, that other ductless glands become involved either in over- or in underactivity. This disturbance of other ductless glands, as diagnosed by the hormonic signs and symptoms, evidenced in the individual case, requires **additional treatment directed toward the secondary involvement of the glands affected.** For instance, late in the course of many hypopituitarisms there is additional hypothyroidism, which is as essential to treat as a primary disturbance of the pituitary gland. In fact, it has been the custom of the writers in more recent observation, first to institute treatment directed toward the secondary glandular dyscrasia. This is done in order to substantiate the diagnosis regarding their involvement, and in this way either include or exclude them as possible complicating factors and consequent cause for therapeutic indications. For illustration, in these advanced cases of hypopituitarism in which there is associated a late hypothyroidism, thyroid treatment is given in order, first, to prove the correctness of the diagnosis of secondary thyroid insufficiency, and, secondly, to eliminate this factor from the field by properly balancing the thyroid insufficiency before the pituitary treatment is given. In this way, the other ductless gland dyscrasias are overcome before the primary pituitary insufficiency is treated, and this gives a clearer insight into the entire case, as to both diagnosis and treatment. Those cases without pituitary neoplasm, which have been treated for a considerable length of time on glandular treatment without any definite results, should be considered as possible **surgical** cases. The time has probably not arrived when radical treatment in the line of decompression operations of the sella turcica can be instituted early in those cases of pituitary disease which do not have definite evidence of an enlarged gland or intracranial pressure symptoms. This is due to the present lack of accurate diagnosis and our ignorance of the future courses of these cases. The inclination at the present time is to believe that many of these cases of the primary pre-adolescent type of unilobar insufficiency of the hypophysis will run a benign course throughout life, *i.e.,* that they will never develop pituitary neoplasm or serious sequelæ. It will require prolonged study of a large number of these cases to determine how many, later in life, change into neoplastic conditions of the pituitary, producing fatal intracranial disease. Of course, as long as this malignant change does not occur, the patient is subjected only to the inconvenience of the statural deformities, to which a great majority of the patients become resigned, rather than accept surgical interference which might entail some chances of recovery. In those cases of bilobar involvement not reacting to glandular therapy, which do not have definite enlargement of the sella turcica, but do have minor localized pressure upon the uncinate lobe or other portions of the brain, producing epileptiform attacks or other intracranial disturbances less severe than those of a definite brain tumor, one is justified in recommending surgical treatment *early in the course of the disease.* The diagnosis in these cases should be so unquestionable that surgical intervention will ensure a good result. They should also have the advantage of correct glandular treatment, properly given for a considerable length of time, before these recommendations are made. Other **associated diseases**, such as lues (Case XI), should, of course, receive the **regular treatment** for such disease. It has been observed that the treatment for the associated disease alone, without concomitant treatment for the hypopituitarism, does not produce relief of the primary hormonic disturbances of the pituitary gland. *Pituitary treatment of such hypopituitary individuals as are later infected with syphilis should go far toward making the course of their lues more benign and latent.*

As stated in previous chapters, other treatment for their obesity and constitutional symptoms resulting from secretory disturbances of these lobes of the pituitary has certainly been unproductive of any result, and it is unnecessary to go into detail with regard to their exhibition. *X*-ray and radium therapy play no part in these complete insufficiencies of the entire pituitary gland. Both of these agents would undoubtedly produce more inactivity of function and decrease in secretion, the effects which are exactly opposite to those which should be produced for good results.

Prognosis.—To date, the prognosis in these cases must be admitted to be unfavorable. First, the late diagnosis, and, secondly, the unsatisfactory treatment as developed to-day are accountable to a large extent possibly for the unfavorable prognosis. In over 50 per cent. of the bilobar cases treated by the writers, without neoplastic involvement of the pituitary gland, very good results were obtained with glandular treatment, given as previously recommended. Some cases were almost completely cured, *i.e.*, there was relief of their constitutional symptoms, consisting of various headaches, thoracic disturbances, dyspnea, syncopal attacks, gastro-intestinal and abdominal symptoms (nausea, vomiting, ballooning, and constipation), pain in the back, and various myalgias. Besides this, the other objective hormonic signs, as obesity and marked disturbance of the function of the gonads, particularly amenorrhea and sterility (one case), have been almost completely corrected. The writers freely admit, however, that in the remainder of at least 50 per cent. of the cases which they have had the opportunity to treat, many of them very energetically and completely for a considerable length of time, absolutely no effects of treatment were noticeable. Among these cases were those in which the diagnosis seemed to be as certain and positive as the simple, pure bilobar hypopituitarisms, in which other ductless glands were only secondarily involved. There is more than a likelihood that the proper treatment was not instituted, or that the diagnosis was wrong and other ductless glands were more decidedly involved, preventing the favorable reaction observed in other cases. The limited amount of success in the few cases in which good results were obtained has been very encouraging as regards the ultimate prognosis. More decidedly effective treatment will unquestionably occur with an increase in the diagnostic acumen and a better understanding of the dosage and combination of polyglandular substances indicated in each individual case. In those cases in which an ultimate complete good result was not accomplished, there was frequently marked alleviation of individual symptoms, which was sufficient in itself to warrant the observation and treatment and the further attempt to relieve the hormonic signs which had not been effected.

Pathology.—The pathology in these cases could not be given because there was no control in the way of local changes in the pituitary itself, or other organs of the body. One can only suspect, from the clinical aspects of the cases, that there was probably the same hypoplasia in both lobes of the pituitary gland which has been found in other cases of this group which have been controlled. There is a question whether the retardation of growth of the skull, *producing a small sella turcica, in itself does not, by preventing the growth and development of the pituitary body, have some effect upon the secretions of the hypophysis contained in this small bony cavity.* This has been the argument advanced for a decompression of the anterior wall of the sella (through the trans-sphenoidal route), in order to allow the gland to increase in both function and secretion. The clinical signs in these cases will show absence of decided changes in the other ductless glands in Case X, and some evidence of hypothyroidism in Case XIII. The ordinary changes found in insufficiency of both the anterior and posterior lobes, in the osseous and dermal systems, were present in both cases, more marked in Case X than in Case XIII. There was a marked decrease in the size of the small, flat bones in both cases, and absence of development of the long bones in Case X, which was not present in Case XIII. The classical adiposity was present in both cases, and need not be referred to in detail. The evidence of absence of hormonic secretions in the ovary is well proved in Case X, as shown by the histological specimen of the ovary. This is important to note on account of the fact that many of these cases are operated upon for mistaken diagnoses, and that the ovary is considered normal on account of its average size and external appearance. Neither of these cases had any clinical evidence of changes in the thymus, such as frequently accompany those cases occurring later in life, as was described in the discussion on Postadolescent Bilobar Hypopituitarisms. In these later cases there is complaint of substernal pressure and subjective dyspnea, which is taken to indicate possible enlargement of the thymus gland, commonly associated with hypothyroidism. There was a spasticity of the colon in Case X, which was at first held responsible for the abdominal pain and distress. On account of the inability to relieve these abdominal symptoms by antispasmodic treatment, this was forsaken as a cause for the abdominal symptoms. The uterus in 2 of these cases was not typically infantile, as in those early pre-adolescent cases of primary anterior lobe insufficiency (Case I). The fact that the 3 cases had periods of imperfect type and irregular intervals is evidence that there was not complete hypoplasia of the ovaries. The blood showed the ordinary lymphocytosis, without eosinophils. The skin in Case XIII was like that ordinarily found in hypothyroidism. This was proved to be of such origin by the effect of thyroid treatment. There were no lesions of the special sense organs. While there was considerable complaint of the eyes in Case X, numerous ocular examinations failed to reveal any hemianopia, lesions of the optic nerve, or of the second, third, and sixth nerves.

SECTION 8

PITUITARISM WITH MARKED CONSTITUTIONAL SYMPTOMS

(*Bilobar Insufficiency of the Postadolescent, Aneoplastic Type*)

This chapter is allotted to the discussion of the very decided *distressing and incapacitating constitutional symptoms usually present with bilobar insufficiencies of the hypophysis occurring late in adult life.* The presenting symptoms in these cases of hypopituitarism consist of such ordinary complaints as severe periodical *headache, vertigo,* subjective *dyspnea,* marked *substernal pain and pressure, nausea, vomiting, abdominal distention* and tympanites, *constipation, lumbago,* etc. It is rare that they seek relief for their obesity, scanty menstruation, sterility, or impotence, which usually go to complete the picture of their hypopituitarism. On account of the late occurrence of the insufficiency of the pituitary gland in these cases, producing an enormous obesity, they are most frequently mistaken for hypothyroidisms. It is true that the thyroid gland usually becomes insufficient sooner or later as a complication of the pituitarism in these cases. That they are not pure hypothyroidisms is proved by the lack of beneficial results from thyroid therapy, as is illustrated by the effect of such treatment in Cases XIV and XV.

Etiology.—There is no evidence of definite etiological factors in any of the following cases, except that of hereditary tendency, which was definitely displayed in the family history of each case. Marked ductless gland dyscrasias, particularly those referable to the pituitary gland, are present in each history. The nephew of Case XV (Case VII) has been described in Section 5 as typical of bilobar pre-adolescent hypopituitarism. The history of lineage in Case XIV also shows marked thyroid dyscrasia, tending either to infantilism or to overgrowth of the skeleton, with obesity. The histories of all these cases are free from any active etiology in the form of infection or trauma.

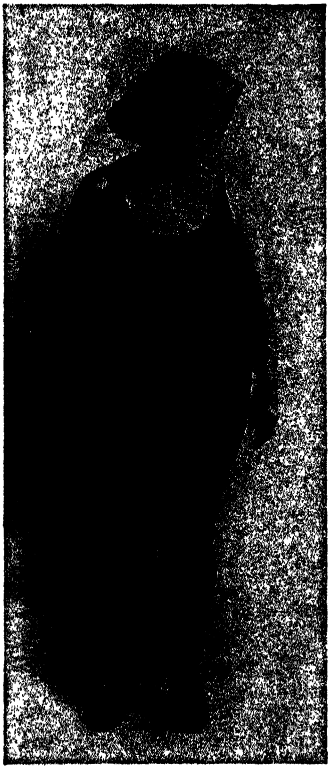
Symptomatology.—HISTORY: CASE XIV.—Miss M. O. S., aged twenty-five, came under observation March 18, 1910.

Present.—Chief Complaints: (1) *Syncopal attacks,* four or five daily. (2) *Extreme headache,* vertex, bicranial location, not associated with ocular or gastric disturbances. (3) *Extreme dyspnea,* paroxysmal, associated with marked substernal pressure. (4) *Severe, intermittent backache.* (5) *Constipation,* associated with sudden attacks of "ballooning" of the abdomen. (6) *Enormous obesity.* (7) *Amenorrhea,* complete for six or eight months; intervals, interspersed with irregular, scanty menses. (8) *Sudden attacks of extreme nervousness, irritability,* frequently accompanied by "*nervous chills.*"

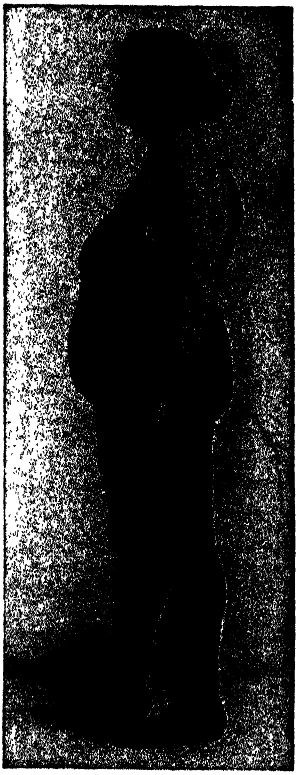
Duration.—The condition had lasted for twenty years.

Course.—(*a*) *Onset:* Insidious. Menstrual disturbances from adolescence at the age of fourteen. First few menses were regular, but scanty, three or four days in duration, flow not requiring more than one menstrual pad daily. *Intervals between menses were from six to eight months.* Periods that did occur during the following three years lasted *only two days,* and *consisted of only a very slight flow,* not associated with dysmenorrhea. Soon after the appearance of the menses, the patient began to have her first attacks of "*fainting.*" A few of these syncopal attacks had occurred previous to her maturity, but they were markedly increased in severity and frequency following this age. The patient's stature at this time was thin and tall. The estimated weight at maturity was 145 pounds.

(*b*) *Progress:* This intermittent amenorrhea, associated with attacks of vertigo and syncope, continued to the age of twenty, the longest interval between periods being eight months, the frequency up to this age averaging three periods a year. At about the age of sixteen the patient first began to be markedly constipated, and noticed the onset of very sudden "ballooning of the abdomen." During these attacks she would frequently have localized swelling of the lips and the buccal mucous membranes of the mouth. The sudden attacks of abdominal distention were so extreme that the patient would be compelled to remove her corset and lie down for comfort. Soon after this, very sudden attacks of dyspnea, associated with a sensation of marked substernal pressure, lasting from one-half to three hours, began to occur. These attacks for a time were associated with ballooning of the abdomen, at other times with her syncope. Many, however, occurred independent of either of these other disturbances. Between the ages of eighteen and twenty, the syncopal attacks became as frequent as four or five times a day. They were not associated with clonic or tonic contractures of the body, and never were accompanied by loss of consciousness, nor followed by sleep. During the entire period from the age of maturity to the age of twenty, the patient had frequent attacks of very extreme headache. This consisted of a sensation of extreme pressure and fullness of the head, which was not localized, and was never associated directly with ocular or gastro-intestinal disturbances. The *entire combination*—headaches, syncopal attacks, dyspnea, and ballooning of the abdomen—*occurred more frequently during the premenstrual week.* These various attacks or combinations of the same were greatly exaggerated and occurred more frequently during the long periods of amenorrhea. They were also apparently relieved or absent for a number of weeks following the scanty, imperfect period. The patient was able to tell when the period was coming on by the severity of some of the above symptoms, previous to its arrival. The backache, general nervousness, and so-called "nervous chills," occurred periodically during this time, either alone on in combination with the other attacks mentioned, and had similar relation to the infrequent menses. Four years previous to the first observation, at about the age of twenty-four, she first noticed the *onset of rapidly increasing obesity.* This deposition of subcutaneous fat occurred first about the hips and the bust. Following its advent, the periods became more irregular and the associated symptoms more frequent and severe.



CASE XIV. Fig. 1.—Note Good Osseous Development, Denoting Normal Pre-adolescent Anterior Lobe Activity. Obesity of Girdle Type.



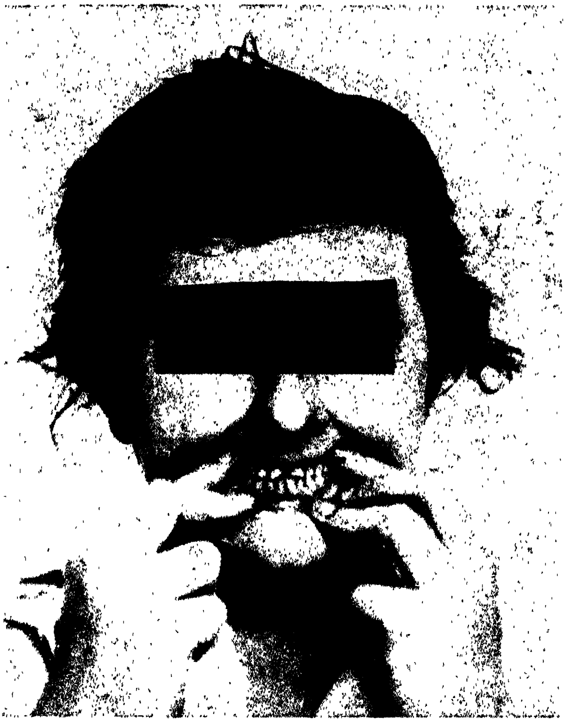
CASE XIV. Fig. 2.—Lateral View, Showing Girdle Obesity, Prominence of Lower Abdomen, Obesity of Upper Thighs, Comparative Slenderness of Lower Legs, and Absence of Cuffing About Wrists and Ankles.

Past.—No injuries, accidents, or operations. Occasional recurrent diseases, such as bronchitis and mild rheumatic pains.

Personal.—Personal history practically negative, with the exception of the menstrual disturbances, as given under Present History.

Family.—Father well-proportioned man, of medium height and build. Mother short, and inclined to be obese, particularly about the hips. One sister of medium height, 5 feet 6 inches, also obese, had apparent enlargement of the abdomen, during which time she was incorrectly pronounced pregnant by one physician; has been married six years without conception. One brother, 5 feet 11½ inches in height, weight 196 pounds. Two other brothers, each about 5 feet 10 inches in height, one weighing 175 pounds, the other, 200.

Examination.—*General.*—Unusually obese woman, 5 feet 8 inches in height, with very *small head, hands, and feet* as compared with the rest of the body. *Obesity localized absolutely to the girdle region,* from the navel down to the junction of the second and lower thirds of the thigh. *Lower portions of the thigh, leg, arm, and hand are unusually slender and free from subcutaneous adiposity.* Neck long and slender, free from fat pads, supraclavicularly or posteriorly. *Head typically pituitary in type,* well shaped and formed. Nose long, bridge straight, tip pointed. Chin well developed, sharp. *Upper incisors decidedly separated. Slight chloasma about the forehead, angles of the jaw, and lateral aspects of the neck;* no other pigmentations. Absence of abnormal distribution of hair, hair of the mons slight (line straight), no hair on the abdomen or chest, comparatively small amount in the axillæ. No abnormal position or gait. Station straight, erect, with tendency to pendulous abdomen, slight lordosis. *Pulse, very slow,* regular, equal, symmetrical, low volume and tension. No edema, cyanosis, or dyspnea



CASE XIV. Fig. 3.—Note Marked Separation of Upper Central Incisors.

during examination. Temperament, psychoneurotic. Measurements: Height, 5 feet 8 inches (173 cm.); circumference of head, 24 inches (61 cm.); of neck, 14½ inches (37 cm.); bust, 44 inches (112 cm.); waist, 37½ inches (95 cm.); girdle, 48 inches (122 cm.); distance from head to symphysis, 31 inches (79 cm.); from symphysis to feet, 37 inches (94 cm.); length of humerus, 12½ inches (32 cm.); forearm, 10¼ inches (26 cm.); femur, 18 inches (48 cm.); tibia, 17 inches (43 cm.). *Weight, 238 pounds.*

CASE XIV. FIG. 4.—NOTE SMALL SELLA TURCICA.

Regional (Positive Physical Signs).—*Head:* Small, well proportioned. *Eyes, ears,* and *nose:* Classical in shape and properly located to make up the typical pituitary head and face. *Face:* Chloasma on the forehead, at the angles of the jaw, and on the neck; very slight lanugal hair on the upper lip and anterior to the ears. *Mouth:* Toothline very straight, separation of the upper incisors, no overcrowding of the lower anterior teeth; very few teeth have small fillings, gums in good condition. *Neck:* Thyroid gland not enlarged, no supraclavicular or posterior cervical fat pads. *Chest:* Unusual development of the mammæ, which are pendulous, glandular tissue making up a comparatively small part of their substance. *Heart,* negative. *Abdomen:* Visceral examinations negative. *Vaginal:* Uterus of normal size and position, vulva fairly well developed.

Laboratory Findings.—*Urine.*—Single specimen, color amber, reaction acid, specific gravity 1.006. Albumin and dextrose negative. Microscopic: Occasional leukocyte.

Blood:	
Erythrocytes	5,090,000
Leukocytes	6,400
Hemoglobin	104 per cent.
Wassermann	negative
Differential count:	
Neutrophils	44 per cent.
Lymphocytes (large and small)	53
Transitionals	3
Chemical Blood:	
Blood-sugar	0.080

Special Examinations.—*Roentgenogram of Head.*—*Sella turcica small,* anterior and posterior clinoid processes almost meeting. Other markings normal.

Ocular Examination.—Fundus negative, perimeter chart normal.

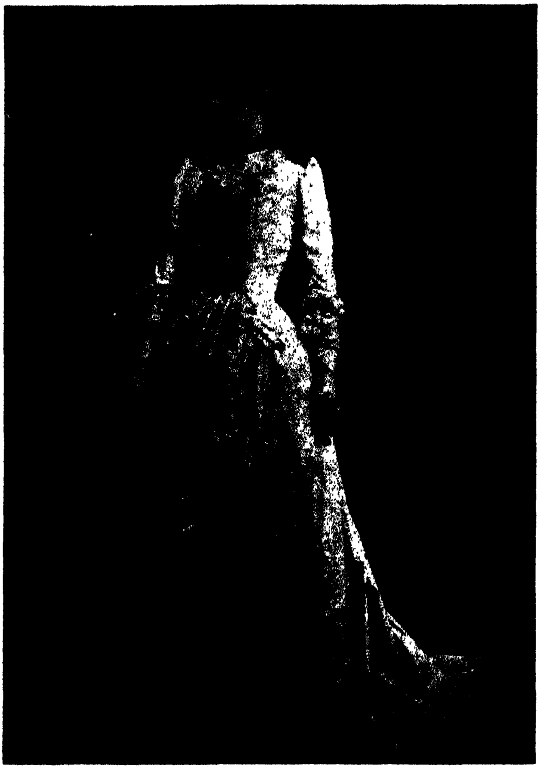
Subsequent Course and Treatment.—Six years ago the patient was placed on **thyroid** and **ovarian treatment,** the ovarian treatment consisting of ovarian extract given by mouth. This treatment had no effect, although it was taken consistently for two years. Later she was given, for a series of six to eight months each, treatment consisting of, first, **posterior pituitary substance** subcutaneously, then **anterior pituitary substance** subcutaneously, and next **a combination of posterior substance and adrenalin,** 7 minims (0.42 c.c.) each, subcutaneously. These injections were given every seven days. No notable improvement or marked change was observed during the year and a half that the patient received this treatment. Then treatment consisting of **individual lobe of the hypophysis** and **posterior lobe combined with adrenalin** was given. Following this, during the past two years of observation, treatment consisting of **anterior lobe of the pituitary, adrenalin, and corpus luteum,** was given subcutaneously, one injection a week, combined with **thyroid,** grain 1 (0.065 gram), and **corpus luteum,** grains 5 (0.3 gram), given by mouth three times daily. Under this treatment the patient noticed very decided improvement. Nearly all of the constitutional subjective symptoms have disappeared. The patient has been practically free from headache, dyspnea, bloating sensation, and syncopal attacks during the past year. Soon after this treatment was begun, the periods began to be more regular, occurring nearly every month; and during the past year the patient has missed only one period, and that during an interval of four weeks when she had received no subcutaneous injections. During this time there has been one relapse, consisting of a slight bloating attack and pain in the back. After the periods had been constant for twelve months, the intervals between injections were increased to two weeks (instead of one). The patient continued to take **thyroid and corpus luteum** by mouth. During the past three months, one hypodermic a month and daily oral treatment as stated above, have been given, and the patient has been completely free from symptoms, with normal periods, lasting from four to six days. During the past year she has lost 43 pounds. Her abdominal measurements are smaller and other changes in size have occurred.

The 2 following cases of hypopituitarism, bilobar variety, neoplastic type, are reported herewith on account of their being almost identical counterparts to Case XIV.

HISTORY: CASE XV.—Mrs. C. W. T., aged forty-three, St. John's Hospital, General No. 22, October 7, 1917.

Present.—Chief Complaints: (1) *Headache,* severe in character, shooting. At times sensation of heavy pressure from within outward, affecting principally the temporal regions, also the supraorbital and occipital regions, shifting in character. Almost constant *aching pain over both eyes,* relieved to some extent by shutting the eyes, with consequent freedom from photophobia. (2) *Severe pain in the lumbosacral region,* particularly in the region of the left sacro-iliac joint, radiating down the leg. (3) Occasional *severe pain in both iliac regions,* intensified by sudden change of position and relieved slightly by bowel movement. Pain is shifting in character. (4) *General hypersensitiveness,* hyperesthesia over the entire body. Picking up skin or pinching of muscles productive of pain. Tendency to bruising. This hyperesthesia affects the skin particularly in the form of pricking paresthesia over the entire body, irregular in distribution. (5) *Insomnia during the night,* but *marked somnolence* at times *during the day.* The patient goes to sleep while reading, and at the table has gone to sleep while eating, particularly certain foods (?). (6) *Transient swelling and distention of the neck,* associated with choking sensation and *marked dyspnea,* making breathing almost impossible. Some *cyanosis.* During these attacks, the patient is unable to lie down or even to sit up, is forced to hang over the edge of the bed in order to breathe. (7) *Increased nervousness,* physical and mental—physical *tremor,* increased irritability, tendency to worry, some emotional instability, no apprehension. (8) *Intermittent polyuria* and *decided polydipsia,* but no marked polyphagia. (9) *Some visual disturbance,* diminution of visual acuity; but the patient is confident that her vision is better in the temporal fields than in the nasal fields. (10) Marked *dyspnea after exertion,* breathing better in the supine position. (11) *Gastric disturbance* immediately *after meals—severe pain, eructations.* The patient is easily nauseated, but rarely vomits. (12) Some *tendency to constipation. Mucus frequently noted,* movement forcible, expulsive, with considerable flatus. (13) ***Markedly irregular menstrual history—periods of amenorrhea as long as nine months,*** marked *dysmenorrhea,* tendency to scantiness (fairly regular in the past four months). (14) Occasional *edema* of the legs. (15) ***Rapid change in both stature and weight*** in the first six months following marriage. (Married at the age of eighteen.)

Duration.—Somewhat indefinite, perhaps dating back for the most part to puberty, which occurred at the age of sixteen.



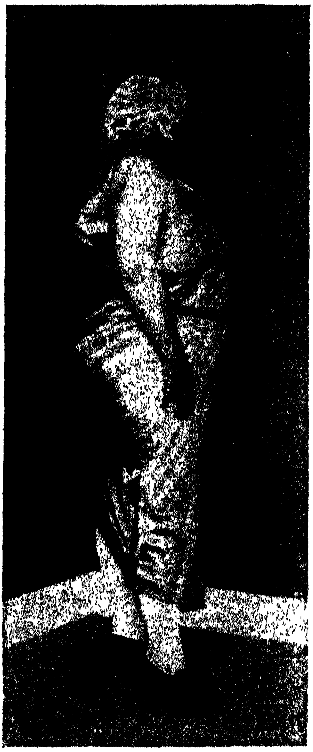
CASE XV. FIG. 1.—NOTE SLENDER, GRACILE TYPE OF MAKEUP, PRECEDING ONSET OF PITUITARY DEFICIENCY.

Course.—(*a*) *Onset:* The patient remembers having had headaches, vague disturbances, pains, hyperesthesia, etc., even previous to that time, but these have been more marked since the menstrual onset. At the age of eighteen, two years following puberty, during which interval the periods had been very irregular, with marked dysmenorrhea, requiring (?) dilatations to bring them on, and considerable amenorrhea, the patient was married. Within six months following marriage, she began to notice decided changes in stature, applicable to height, but particularly to obesity. This *obesity* was *of distinct limitation,* of the *girdle* *type,* the fullness affecting the abdomen and hips. The upper portion of the body, the mammæ, and the lower portions of the limbs escaped this increase in size. At the age of eighteen, the patient wore a No. 18 corset. The exact increase in the size of the corset was not noted, but there was a decided and definite increase. There was a rapid increase in weight, exact amount not known (previous weight, 140 pounds). After this primary increase, the weight remained practically stationary until about eight years ago, when another remarkable increase occurred. The weight at this time was 237 pounds; exact amount of gain at this time not recalled.

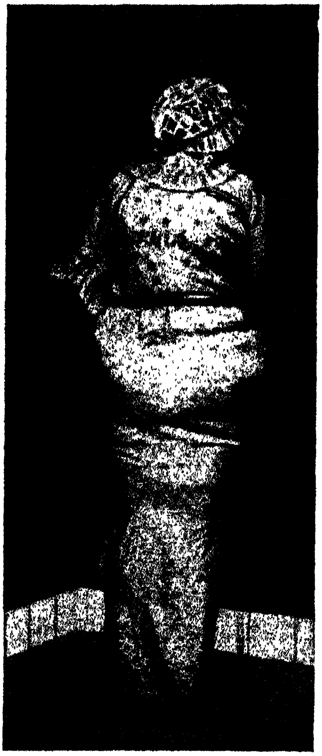
(*b*) *Progress.*—The patient was in the hospital at this time five weeks, under the authors' observation, and was given thyroid in large doses, *reaching a maximum of grains xv* (0.972 gram) *daily; despite this energetic treatment, the patient continued to gain weight consistently and rapidly.* One effect of the thyroid treatment that continued for some time was regulation of the periods. *Pituitary treatment* was used *following thyroid treatment, without effect upon the obesity.* The varied complaints mentioned above under Chief Complaints date back particularly to the first increase in weight and stature, particularly the severe headaches, affecting the occipital, supraorbital, and temporal regions, and almost constant. At times there is a sense of "inward pressure," associated with hot flushes. Many of these symptoms—pain in the back, indefinite pains in the abdomen, sometimes in the right, sometimes in the left side, attacks of dyspnea whereby the patient is forced to lie over the bed with her head down to breathe (associated with choking sensation and a swollen, distended condition of the neck), hyperesthesia, paresthesias of various sorts, and somnolence—are of indefinite origin, the patient being unable to trace them back clearly. The patient is inclined to date them to the age of eighteen, but is of the opinion that a number of the nervous manifestations have been of more recent date. Eight or nine years ago, when the second increase in weight occurred, at which time the patient was under the writers' observation, many symptoms were increased in severity, particularly the nervous manifestations (at that time was in bed for five weeks for nervous prostration). Increased irritability, worry, and emotional instability have been more severe in the past four years. The drowsiness, which at times causes the patient to fall asleep while eating, or after eating certain kinds (?) of food, is of indefinite duration. *The tendency to intermittent polyuria and polydipsia is also of indefinite duration* (the patient states years); more decided in recent months. The gain in weight over these years, despite the sudden increase, has been consistent, with some tendency to girdle obesity and marked prolapse of the lower portion of the abdomen. In the past few months the nervous symptoms have all been intensified. For the past eight or nine years the patient has noticed an *abnormal growth of hair on the lip and under the chin;* no abnormal growth of hair on other portions of the body. No marked history of abnormal pigmentation. No signs or symptoms referable to other systems.

Past.—Measles, scarlet fever, rheumatism, malaria, severe dysentery at the age of seventeen, typhoid fever. Operation for polypi of the uterus. Tonsils cauterized.

Personal.—No coffee, tea moderately, no alcohol (patient very susceptible to alcohol). The periods began at the age of sixteen, always irregular, as noted above, more regular in the past few months than usual. No pregnancies. Appetite good, voracious at times. Some tendency to constipation. Sleeping disturbed during the night, somnolence at other times.



CASE XV. FIG. 2.—SAME CASE AFTER ONSET OF OBESITY.



CASE XV. FIG. 3.—NOTE CHARACTERISTIC GIRDLE OBESITY.

Family.—Father dead, aged sixty-five, nephritis. Mother living, aged sixty-four, neuritis. One brother, one sister living, well. Sister is obese, but diffusely so, with large bust, no tendency to girdle obesity. This sister has three children, one aged fifteen who is remarkably obese (Case VII). No family history of important hereditary diseases.

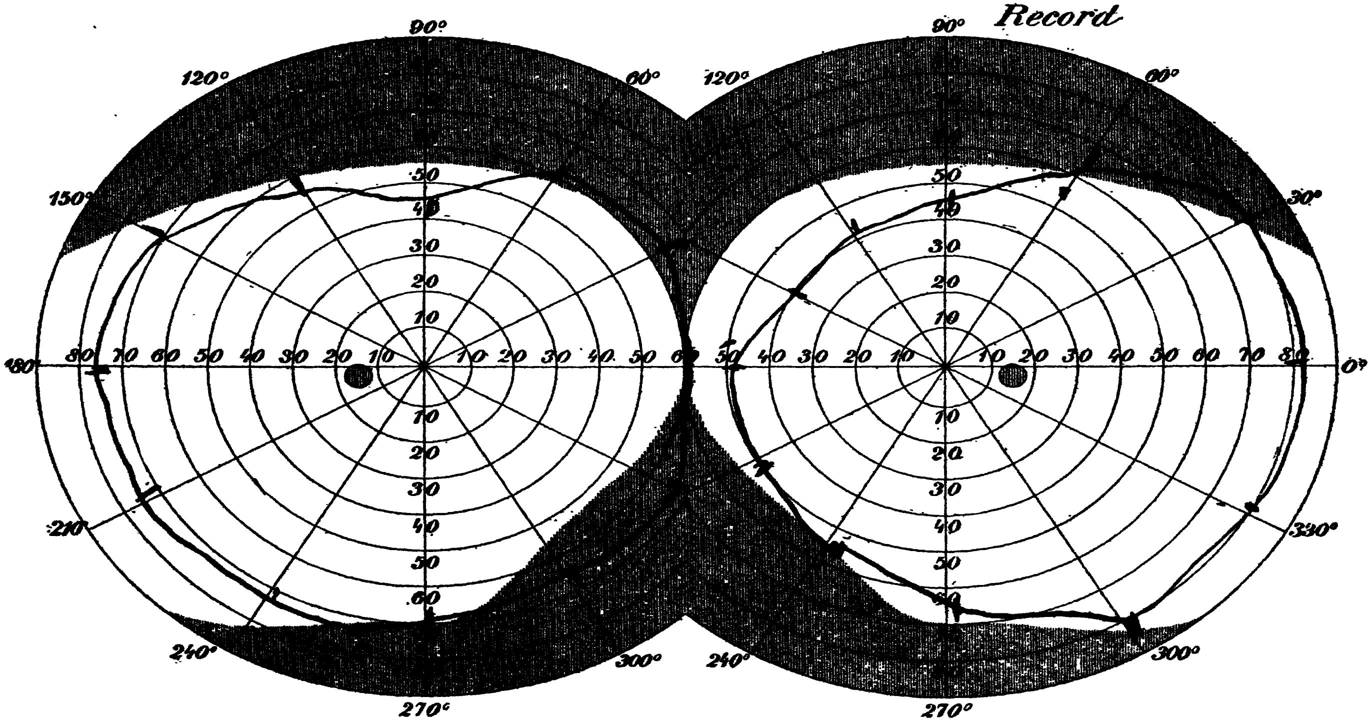
EXAMINATION.—*General.*—*Height,* 5 *feet* 7¼ *inches; weight,* 256 *pounds.* General development very large, tall, obese, with marked disproportion of the long bones. *Small hands and feet,* slight padding of the dorsa of the hands and fingers. There is marked hyperesthesia of the thumb of the right hand, and a similar sensation in the little finger of the left hand. Marked tenderness to slight pressure of the skin, over the entire body, some tendency to easy bruising. Marked abnormal distribution of hair on the lips and maxilla. No cyanosis, dyspnea, or edema. Pulse, moderately slow, good volume and tension, equal, symmetrical, no particular character. Temperament psychoneurotic. *Temperature,* 97.2°-98.2° F. (36.2°-36.7° C.). Measurements: Height, 5 feet 7¼ inches (171 cm.); from vertex to symphysis, 35 inches (89 cm.); from symphysis to soles of feet, 32¼ inches (82 cm.); span, 70 inches (178 cm.); length of humerus, 12½ inches (32 cm.); forearm, 11 inches (28 cm.); femur, 17 inches (43 cm.); lower leg, 16½ inches (42 cm.); circumference of head, 22 inches (56 cm.); at superior maxilla, 20 inches (51 cm.); at inferior maxilla, 18½ inches (47 cm.); neck, 14½ inches (37 cm.); bust, 41½ inches (105 cm.); waist, 37 inches (94 cm.); symphysis, 50 inches (127 cm.).

Regional (Positive Physical Signs).—*Head:* Typical *pituitary type,* large and well proportioned. Slight *brownish pigmentation on the forehead* and the *lateral aspects of the neck and inferior maxilla.* Abnormal distribution of hair about the chin and upper lip, lanugal growth; hair extending from the hairline down on the forehead and on the neck, hairline low; eyebrows thinned at the outer margins. *Neck:* Short and thick, thyroid not enlarged; few small palpable lymph-glands in the left inferior triangle. *Chest:* Tendency to fat padding high in the thoracic region and the cervical region posteriorly, very slight pads below scapulæ, no supraclavicular fat pads. *Heart:* Negative. *Blood-pressure:* Systolic 145, diastolic 95. *Abdomen:* Visceral organs negative; *abdomen very large, pendulous,* with tendency to *greater obesity below the navel,* marked bulging of the flanks, *protrusion above the mons,* producing marked folding and projection of the portion of the abdomen above this fold. Marked striæ, marked padding in both the hypogastrium and the region of the mons. Distribution of hair normal. Diffuse marked superficial and deep tenderness over the entire abdomen. Tympany throughout, including deep in the flanks; no localized rigidity at this time. No localized or purely circumscribed deposition of fat; few pigmented moles about the lower abdomen. *Vaginal:* Vulva very large, redundant, perineum not relaxed. (Impossible to ascertain exact size of the uterus, on account of the marked obesity.) *Extremities; Absence* of marked *obesity in the lower portions of the thighs, legs, the feet, arms, and hands.* The patient states that there has been edema present about the ankles. *Nervous system,* negative.

Laboratory Findings.—*Urine.*—(*a*) Single specimen, color lemon, reaction acid, specific gravity 1.016. Faint trace albumin. Dextrose, casts, leukocytes, and erythrocytes negative. Numerous epithelial cells.

(*b*) Twenty-four hour specimen, 2,300 c.c., pale, reaction alkaline, specific gravity 1.015. Trace albumin. Dextrose, casts, leukocytes, and erythrocytes negative. (Two following twenty-four hour specimens, identical.)

Feces.—Brown, soft. Ova, parasites, mucus, pus, blood negative.



CASE XV. Fig. 4.—Perimeter Chart. Note Very Slight Contraction of Visual Field.

Blood:

Erythrocytes	4,640,000
Leukocytes	7,600
Hemoglobin	90 per cent.
Stained smear	normal
Wassermann	negative
Blood-sugar	0.072

SPECIAL EXAMINATIONS.—*Roentgenogram of Head.*—Frontal sinus small. *Sella turcica small.* No other abnormal markings.

Ocular Examination (by Drs. Swartz and Luedde, October 4, 1917). —Ophthalmic examination revealed nothing pathological. Gradual increase in hypermetropia, which at first was in the region of 0.75 plus, and now is approximately 2.0 diopters for either eye. Perimeter fields show slight contraction.

HISTORY: CASE XVI.—Mrs. J. T. W., aged forty-one, St. John's Hospital, General No. 2498, May 29, 1917.

Present.—Chief Complaints: (1) *General weakness, languor, malaise,* disinclination to effort.

(2) *Intermittent nervousness, irritability, tendency to worry,* tendency to depression and melancholy alternating with spells of euphoria, emotional instability (well controlled).

(3) Slight temperature, maximum 100° F. (37.8° C.) in the early afternoon, rarely after seven o'clock, becoming subnormal after that time, subnormal also in the morning.

(4) No sudden increase in weight at any time, although there have been fluctuations. The patient was slender as a girl. Some *tendency to increase in weight* occurred, *gradual, following the birth of a child fourteen years ago. Some increase in the size of the hands out of proportion to the general gain.* The patient at the time of marriage wore a No. 5 glove, at the present time wears a No. 6, six years ago changing from size 5½ to 6 without apparent increase in the general weight or size. She wore a No. 1AA shoe at the time of marriage, and now wears a No. 2B. *Some increase in the padding over the hips and in the mammary development out of proportion to the general increase. At one time there was some supraclavicular padding, which is not there at the present time.* Some increase in the size of the ankles, reduced by pressure, never subject to indentation or pitting. This has peculiar feeling to the patient, as if thick-skinned; sensation of tension and fullness in the feet and ankles.

(5) Dermal system: *Change in the texture of the hair,* tendency to be coarser, dryer, and brittle, ends breaking off. Some loss of hair, appreciable change in pigment from auburn to a darker brown; very slight loss of pigment, localized on the vertex. *Chloasmic spots on the skin of the hands and on the forehead* just beneath the hairline; some noticed about the shoulders, but none along the ears or on the neck. Some increase in coarseness of the skin texture, to dryer character, with tendency to chapping; some tendency to desquamation at times. For-

merly perspiration was difficult to elicit; at the present time the patient perspires more freely. There has been an *increasd growth of hair about the arms, cheeks, and inner aspects of the legs, and slight growth on the upper lip.* Some chloasma or pigmented spots about the back recently. *General hypersensitiveness of the entire body* and tendency to bruising.

(6) The periods began at the age of fourteen, followed by *amenorrhea for eight months after the first period,* commencing again, *irregular, with six or eight week intervals between the periods.* They were *very profuse, lasting as long as three weeks, very painful.* At the age of twenty-three, following the birth of a child, the periods changed in character, not painful, regular (every month), but scarcely two or three days in duration of flow, remaining so up to the present time. There has been no marked dysmenorrhea since the onset of the trouble. The only change noted has been the scantiness, more marked every other month. *For a week following the cessation of the period,* the patient is *inclined to be more nervous and irritable.* During the period and the post-period time, the *temperature* is inclined to be *either normal or subnormal;* whereas at other times the slight temperature referred to is observed.

(7) No constipation. Gastro-intestinal disturbance,—*severe cramping, below the navel,* confined to the center, not relieved by bowel movement, brought on by cold drinks, ice cream, etc. There has always been a tendency to looseness of the bowels. Since the onset of the trouble there has been no constipation.

(8) *Migraine complex,* independent of the menses, sometimes hemicranial in type, accompanied by nausea and vomiting, but no visual disturbance except photophobia, the patient being more comfortable in a dark room.

(9) *Severe lumbosacral backache,* intensified by lifting.

Duration.—Seven years.

Course.—(*a*) *Onset,* gradual, as feeling of general malaise, weakness, and temperature, as referred to under Chief Complaints. All these special changes noted under Chief Complaints have come on gradually and progressively—increase in size of the hands and feet; distribution of fat about the hips, supraclavicular spaces, and mammæ; changes referable to the dermal system, such as increased growth and distribution of hair, change of previously existing hair in pigment and texture, with some loss, increased perspiration, and tendency to dryness and desquamation of the skin; gastro-intestinal symptoms, cramping and gastric complex; some scantiness of the periods; and changes referable to the nervous system, such as irritability, worry, and depression, in relation to the menses. The patient, when asked how a picture taken seven years ago, previous to the onset of the trouble, would compare with a picture taken at the present time, states that there is a marked difference, a resemblance being scarcely recognizable, her appearance at present, in comparison with formerly, giving an impression of a larger and heavier person, described as a "great, fat woman."

(*b*) *Progress.*—In the past seven years the patient has consulted Dr.

Hugo Summa. A bad prognosis was given, and the patient was placed on a dry diet, with rapid loss of weight, but with no amelioration of symptoms. One year later she saw Dr. B. Sippy of Chicago, who advised open air, fattening diet, and tonic treatment, without change of symptoms.

Past.—Measles, scarlet fever, diphtheria, acute articular rheumatism, typhoid, pneumonia twice, pleurisy twice, la grippe every winter. The patient was exposed to tuberculosis through her father and through the sister of her husband, and was supposed to have had tuberculosis at the age of eighteen. Very slight hemoptysis, probably one-half ounce, six years ago. There is, however, no cough or expectoration at the present time.

Personal.—Tea very moderately, no coffee, wine moderately. Appetite never hearty. Insomnia in the early morning. Bowels regular, with tendency to looseness, as referred to. The patient endures cold better than heat; never complains of being cold except that hands and feet are cold when nervousness is marked.

Family.—Father dead, aged sixty-two; died of chronic tuberculosis. Mother dead, aged sixty-five, heart trouble. One brother living, has heart trouble. Four sisters living, well. One brother died in infancy. Two sisters dead, one possibly of paralysis, one of pneumonia. The patient's mother was forty-seven years of age at the time of the birth of the patient; menstruated regularly during the entire pregnancy. The patient weighed 3 pounds at birth. The living sisters bear no resemblance in stature, general development, or appearance to the patient. No family history of tuberculosis otherwise, or of other hereditary diseases. Mother, father, and one sister had migraine.

EXAMINATION: *General.—Fröhlich type of individual,* rather classical. *Hands and feet comparatively small, long bones not developed.* Considerable amount of *girdle obesity,* mammary glands not highly developed, no fat pads about the shoulders anteriorly, slight amount posteriorly along the folds of the muscles. Very slight pigmentation, *chloasma about the forehead and the angles of the jaw,* some along the malar processes, no abnormal pigmentation on the rest of the body. *Body* almost *entirely free from hair,* line across the mons very straight, no large amount on the extremities. No edemas. *Has had puffiness of the hands,* only very slight indication of puffiness now about the backs of the hands. Obesity does not stop abruptly at the wrist, although there is some demarcation there. Feet look as if pseudo-edematous; no definite marks left by prolonged pressure, some marks of shoe laces seen. No varicose veins, slight dilatation of superficial venules on the extremities. No abnormal gait or station. Pulse, very low volume and tension, normal rate, good rhythm, equal, symmetrical, no special type. Temperament psychoneurotic, fairly well controlled, highly emotional. *Hyperesthesia, diffuse, ecchymosis of the right arm* (*ecchymoses produced very easily*). Two blue spots on the outer side of the left hand, extending from the little finger almost to the carpal bones. *Blood-pressure:* systolic 135, diastolic 85.

Regional.—*Head, neck,* negative. *Chest* and *abdomen:* Visceral organs negative.

LABORATORY FINDINGS.—*Urine.*—(*a*) Single specimen, pale, specific gravity 1.006, reaction acid. Faint trace albumin. Dextrose, casts, leukocytes, and erythrocytes negative.

(*b*) Twenty-four hour specimen, 2,250 c.c., pale, specific gravity 1.000, reaction acid. Trace albumin. Dextrose, leukocytes, erythrocytes, and casts negative.

Feces.—Brown, formed. Mucus, pus, ova, and parasites negative. Occult blood positive.

Blood:

Erythrocytes	4,420,000
Leukocytes	8,000
Hemoglobin	70 per cent.
Wassermann	negative
Blood-sugar	0.132

Stomach Content.—Ewald test meal, one hour in stomach, poorly chymified. Moderate amount of mucus, free hydrochloric acid negative, lactic acid positive, Boas-Oppler bacilli negative.

SPECIAL EXAMINATIONS.—*Fluoroscopic.*—Negative.

Roentgenogram of Head (Transverse View).—Shows sinuses all free from shadows. Sphenoid sinus seems to be divided, with horizontal partition. Sella turcica *very small,* posterior clinoid process only about one-fourth inch from the anterior, bending up sharply forward, entire pituitary fossa not larger than a pea. Entire cranium small, some of the sutures well made out.

Roentgenogram of Chest.—Negative.

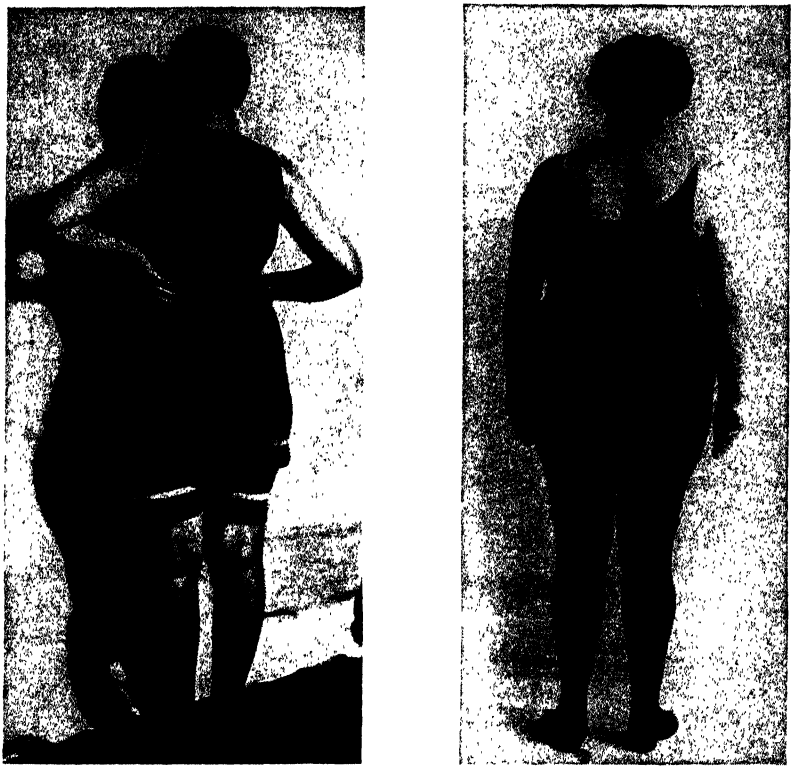
Trochoscopic.—Spasticity of the descending iliac and pelvic colons. Right half of the transverse colon low in the right inguinal region, cannot be moved upward by manipulation.

SUMMARY OF SYMPTOMS.—The most important hormonic symptoms of adult bilobar hypopituitarism as illustrated by these 3 cases are the *very decided constitutional symptoms* associated with postadolescent insufficiency of both lobes of this gland. It is these complaints for which the patients usually seek relief, and not the obesity or the amenorrhea, which are comparatively insignificant as disturbing factors compared with these very severe and frequently incapacitating symptoms. Two of these cases, for instance, were absolutely incapacitated for duties of any kind during years of their early course. They are the most confirmed and frequently bedridden invalids, who, on account of their apparent healthy appearance, receive comparatively little medical observation or attention. The severe chronic headaches and backaches, the marked nocturnal insomnia, and somnolence during the daytime, the extreme nervous instability, paroxysmal dyspnea, syncopal attacks, ballooning of the abdomen, constipation, etc., are so persistent and unrelievable in these cases that, if their association with pituitary disturbances is not well known, they are, in the great majority of instances, treated as local and independent diseases of various organs of the body. It will be noticed that this type, having posterior lobe insufficiency late in life, do not complain of the extreme abdominal cramps and extremity pains which are fairly constant in the cases occurring earlier in life and always present in the hyperactivity of the posterior lobe.

Diagnosis: *Postadolescent Hypopituitarism, Bilobar Variety, Neoplastic Type.*—The general characteristics referring to the hormonic signs in this case are so similar, with one exception, to the pre-adolescent bilobar hypopituitarisms, described in Section 5, Case VII, that it is unnecessary to give detailed reasons for such a diagnosis. The marked disturbance of the menses throughout the entire course, up to the last two years during which the treatment became effective, connects it with an anterior lobe insufficiency. This amenorrhea, associated with the girdle obesity, decreased metabolism, slow pulse, increased sugar tolerance, etc., proves that the posterior lobe was also involved. This combination, with exclusion of all other diseases, is sufficient not only to classify this case as a hypopituitarism, but to place it in the bilobar division of these dystrophies. The effect of simple substitution treatment is additional evidence that the disturbance of pituitary function and secretions was the primary basis for the entire syndrome. The negative effect of the substances of the other *individual* endocrinous organs upon the symptoms, and the absence of the independent hormonic signs of single ductless glands, are diagnostic factors, excluding the thyroid, the gonads, or a single lobe of the pituitary as a uniglandular cause for the clinical manifestations.

As an illustration of DIFFERENTIAL DIAGNOSIS, it is instructive *to contrast the hormonic signs,* particularly the skeletal growth and the amount of obesity, existing *in the pre-adolescent,* with the *postadolescent type of hypopituitarism.* This is best demonstrated by the contrast detailed in a comparison of a primary pre-adolescent anterior lobe insufficiency (Case I), without involvement of the posterior lobe, with the hormonic signs presented by this case (Case XIV).

The most striking difference noted in the comparison of these 2 cases is the *effect of the insufficiency of the anterior lobe upon the skeletal growth.* When this secretion is withdrawn or markedly decreased during the pre-adolescent age, it produces a *very short, arrested growth, affecting all the bones,* as is seen in the stature of Case I. In Case XIV the insufficiency occurred *late in life, after the epiphyseal junctures had closed,* as can be seen by the unusual *length of the long bones and the height of the patient.* Other possible explanations for the overgrowth of the long bones in this case (XIV) might be considered; for instance, hypersecretion of the posterior lobe of the pituitary, whose overactivity is supposed to inhibit the gonads, producing amenorrhea, and a late closure of the epiphyseal junctures of the long bones, allowing them to overdevelop. There is no other evidence, however, that the posterior lobe was overactive during the early stage of the skeletal development in Case XIV. Overgrowth is shown in previous cases (V and VI) under the analysis of the hormonic signs produced by oversecretion of the posterior lobe. The early course of Case XIV was free from such signs as glycosuria, polyuria, emaciation, increased metabolism, etc. The short and acral bones in both these cases (I and XIV) show the evidence of a partial insufficiency of the anterior lobe, which would be suspected from the gonad disturbance. The head, hands, feet, nose, and chin are all very characteristic *in both cases* of anterior lobe insufficiency, which occurred during the early age of their formation. The smallness of these parts and bones is one of the most reliable diagnostic points, showing a tendency to inactivity of the anterior lobe of this gland at an early age. The fact that these parts *permanently remain small,* with their details unchanged *throughout the entire life of the individual,* unless there is a later *overactivity of this lobe of the gland,* producing the consequential changes in these bones and their


A B

CASES I AND XIV, A AND B. COMPARISON OF OSSEOUS DEVELOPMENT OF PREADOLESCENT AND POSTADOLESCENT ANTERIOR LOBE HYPO-ACTIVITY.

In A, note underdevelopment of osseous system and small hands (*see* Case I). In B, note normal osseous development, because of normal early anterior lobe activity; also girdle obesity of classical type.

coverings, makes their size, shape, and form one of the most valuable diagnostic signs referring to the activity of the anterior lobe.

The difference in the obesity in these 2 cases is another striking point that well illustrates the difference between the unilobar and the bilobar type of insufficiency of this gland. In Case I there undoubtedly was an *absence of disturbed function* of the posterior lobe of the gland, throughout its entire course. Although this patient is now thirty-six years old (three years older than Case XIV), there has never been, at any time during the entire course, any evidence of either a hypersecretion, such as polyuria, or a hypo-activity, as obesity or constitutional symptoms, of the posterior lobe. In Case XIV there has been, since the age of twenty, definite evidence of a progressive insufficiency of the posterior lobe, up to the time of its relief by treatment. This is well appreciated by observance of Fig. 4, showing the difference in obesity of the girdle region and of the mammæ. In Case I it will be noted that the mammæ retained their virgin character. In Case XIV the history and examination show the typical marked enlargement and pendulous condition of these glands. Case I shows the complete absence of girdle obesity, Case XIV showing very typical and marked girdle obesity, extending from the navel to the junction of the middle and lower thirds of the thigh. The *absence of subcutaneous adiposity in the lower part of the thigh, leg, arm, neck, and dorsum of the hand and foot, is distinctly shown in both cases.* Metabolic tests also demonstrate the absence of sugar tolerance in Case I, and the marked increased amount of sugar tolerance in Case XIV. The differences in pulse, temperature, nervous and abdominal symptoms, headaches, dyspnea, etc., are very interesting to note. *In the primary insufficiencies of the anterior lobe, all of these constitutional symptoms have been entirely absent,* while in the bilobar involvement in which the posterior lobe is decidedly affected, as shown in Case XIV, *these marked constitutional symptoms have been the most distressing and incapacitating complaints.*

Both of these cases (I and XIV) were negative for neoplastic changes of the hypophysis. A comparison of the roentgenograms in the 2 cases will show, however, that Case I had a very much smaller sella turcica than Case XIV, although the latter could not be considered one which was due to an enlargement of the pituitary gland. There were no intracranial pressure symptoms in either case, although Case XIV complained very severely of recurrent attacks of severe headache.

Complications and Sequelæ.—The most important complication and sequela in 2 of these cases is their tendency to *acute infection.* Case XV, for instance, is almost constantly complaining of re-infection of the nose, throat, or bronchi. Case XIV, during the last two years of observation, has consulted and treated as much for these same infections, particularly rhinitis or bronchitis, associated with a mild arthritis, as for her pituitarism. Two of these patients (XIV and XV) are constantly complaining of chilliness and inability to stand exposure of any kind. This complaint has frequently recurred, in the insufficiency of the posterior lobe, probably due to the subnormal temperature and lack of dermal reaction to external temperature. That there is a polyglandular dyscrasia present in all of these cases at this time is without doubt. The effect of treatment in Case XIV tends to prove that conclusively. There is undoubtedly a secondary thyroid, and probably a secondary adrenal insufficiency, definitely present in this case, as has been shown by the relief of signs and symptoms only after polyglandular treatment, which included substances from both of these glands. The gonad insufficiency markedly present in all of these cases should be considered more as a part of the disease than a complication or sequela, as it is one of the cardinal signs necessary for a positive diagnosis. In Case XV there undoubtedly was much more thyroid insufficiency than in Case XIV, as is shown by the marked thickening and dryness of the skin and the subdermal infiltrations present throughout the entire body. During the course of this case, the marked somnolence which is present as noted in the history, is indicative of concomitant thyroid with pituitary posterior lobe insufficiency. The writers have noted this in other cases of posterior lobe insufficiency. Unless there is a decided additional thyroid insufficiency, the somnolence or torpidity is usually less marked. This somnolence occurred very characteristically in this case during the daytime, and was replaced during the night by restlessness and insomnia. Sterility and frigidity might be considered as sequelæ or complications in these diseases. Case XIV is unmarried, but never developed any signs of sexuality. Case XV has been married twice, with very little sexual desire and with a negative history of conception.

Associated Diseases.—The marked decrease in the metabolism, associated with the subnormal temperature and slow pulse, makes this type of individual less resistant and consequently more susceptible to infectious diseases. The course of these cases while under observation helps to prove this point. They have suffered from repeated re-infections of the respiratory tract throughout the winter months. They are very much more comfortable during the summer and are freer from infection during this season, although they do not bear the extremely warm weather particularly well. Their constant complaint of chilliness and lack of endurance to slightest exposure is undoubtedly due to their subnormal temperature and absence of dermal reaction to external temperature changes. Case XIV was treated repeatedly during the past two years, even after there was no reaction to the treatment for hypothyroidism, for rhinitis, bronchitis, and mild rheumatic attacks. It is unlikely that this type of individual (hypopituitarism, particularly of the posterior lobe) is as susceptible to rheumatic fever as is the hypothyroid individual. Yet even in these pituitary cases reacting favorably to treatment, it is quite noticeable that they are more or less constantly complaining of mild local or general infections. As has been stated above, it has been the writers' experience with other cases, of the male sex, who have been infected with syphilis, that they are inclined to have very early cerebrospinal lesions, bearing out Draper's contention of the susceptibility of this as well as other diseases of internal secretory unbalance.

Clinical Varieties.—The anatomicophysiological varieties have been so frequently discussed in previous chapters that it would be only repetition here to go into detail with regard to classification of these cases. There is undoubted evidence in all of these cases of an insufficiency of both the anterior and posterior lobes of the pituitary gland, in which the posterior lobe insufficiency occurred after the age of twenty. It is probably a striking coincidence that the evidence of posterior lobe insufficiency in Cases XIV and XV occurred at about the age of twenty. Photographs of Case XV previous to her marriage show that there was no evidence of posterior lobe insufficiency. Their menstrual disturbances, indicating anterior lobe insufficiency, are also very similar. They both had prolonged periods of amenorrhea, interspersed with scanty menses, dating almost from the age of maturity. This marked similarity of the inactivities of both of these lobes probably accounts for the marked similarity in the general makeup of these two individuals. Both have practically the same height, the same amount of obesity, the same general configuration, proportions, stature, etc. The laboratory and special examinations in both these cases are the routine reactions observed in the insufficiency of both lobes of the pituitary, and need not be restated. It will be noted from the physical examination and the skiagram that the entire head, the sinus, and the sella turcica measure almost the same in both cases. The sella turcica was not enlarged in either case. This, taken with the absence of intracranial pressure symptoms, classifies both of these cases among the aneoplastic types.

Treatment.—PROPHYLACTIC.—It is only necessary to say with regard to prophylactic treatment that the early diagnosis in these cases is absolutely essential for its proper exhibition. Those families having these pituitary tendencies should be given special attention with regard to the development and maturity of their children. It is more than likely that if these cases were recognized before maturity, a great deal more could be accomplished with regard to preventing the enormous disproportions of the individual, as well as a great mass of very distressing secondary constitutional disturbances resulting from the unbalance of pituitary secretion. A better understanding of the relation of infectious diseases and of trauma to the pituitary dyscrasia, would also stimulate more investigation and observation following these etiological factors, concerning particularly typhoid and head injuries, which may be the beginning of these very serious diseases.

ACTIVE TREATMENT.—In these cases which are *not associated with pituitary tumor*, the treatment should be **medical** for a considerable length of time. The encouraging result obtained by the writers in their limited series of cases has convinced them of its efficacy. As has been stated in a previous chapter, 50 per cent. of the pituitary insufficiencies have been very decidedly improved after the proper combination of **glandular extracts** has been exhibited. Case XIV illustrates the difficulties and the exceedingly long time required to determine just the right combination of treatment that is required for the individual case in order to finally accomplish results. The most important fact in the treatment of this case was the recognition that it was really, at the time of observation, a *polyglandular disease.* It is the writers' plan to consider these diseases as primary disturbances of one gland, with secondary dyscrasias of other glands, merely to impress the necessity of the diagnosis of primary conditions, as well as of secondary endocrinous disturbances. That these cases (XIV and XV) were not due primarily to thyroid insufficiency has been proved by the negative effect of treatment which was originally given to each case. In Case XIV **thyroid treatment** was given for almost a year, without any perceptible effect upon the signs or symptoms. In Case XV, excessive doses of thyroid gland—grains xv (0.972 gram) a day—were given for a number of weeks in succession, without any loss of weight or other effects upon the obesity, *but, on the contrary, with an absolute gain in weight while under this treatment.* Yet after thyroid medication was combined with other ductless gland substances, in Case XIV there was marked decrease in weight and a very decided effect upon the *constitutional symptoms* as well as upon the *amenorrhea.*

These 2 cases, while apparently so very similar with regard to their clinical makeup, as will be noted from the history, were entirely different with regard to reaction to treatment. In Case XIV there was finally obtained a very decided and complete reaction to **polyglandular** treatment, whereas in Case XV the effect has been only a very slight one, affecting only partially the constitutional symptoms and the amenorrhea. This case also failed to react to treatment of individual glandular products, such as thyroid, pituitrin (posterior lobe), ovarian extract, and corpus luteum, given successively, *one at a time,* by mouth, over long periods, varying from eight to twenty months. It has been the writers' experience that these preparations *given by mouth alone* have not been effective in controlling or even modifying any of the hormonic signs present in pituitary disease. In fact, it was only after different preparations had been used, subcutaneously or intramuscularly, in conjunction with glandular therapy by mouth, that any definite result was obtained with organotherapy in these diseases. The failure of a reaction in Case XV is thought to be due to the inability to follow the indications presented by this case. There is undoubtedly a very decided deficiency of both lobes of this gland present. Yet the patient received only comparatively small subcutaneous doses of these lobar preparations, at long intervals (not oftener than one in seven days). It has been only for the past six months that this patient has been placed upon what is now considered rational polyglandular treatment, more adapted to the actual deficiencies of the many glands involved. Even the slight improvement which has taken place under this treatment has been most encouraging, and the writers have hopes of yet affording more relief pertaining to the obesity and the recurrence of constitutional symptoms which have been present to date.

Indications in these *insufficiencies of both lobes of the pituitary, with secondary inactivities of other endocrinous glands,* particularly the thyroid, the adrenals, and the gonads, must of necessity be an attempt to **substitute** these **glandular secretions** in just the correct amount to restore the internal secretory balance. Any one who has attempted to do this will surely admit that it is a problem requiring a very considerable amount of time, patience, and study. Each case unquestionably is a problem in itself. These 2 cases, both of which have been under observation for over six years, one yet very imperfectly relieved, are good illustrations of the persistence required if good results are ultimately to be obtained. The fact that one case (XIV) has been so completely relieved of all the symptoms, and that the other case (XV) has during the past six months begun to react favorably to a combination of ductless gland substances, demonstrates what might possibly be accomplished in other cases apparently as refractory and difficult to treat.

The original plan of attempting first to substitute the deficient secretions of endocrinous glands which might be secondarily involved, is still considered the best plan of initiating the treatment. While neither of these cases has reacted to ovarian or to thyroid therapy, the writers have had a number of cases in which there undoubtedly was a decided insufficiency of the thyroid, as proved by the partial reaction to this treatment in the reduction of the obesity, somnolence, menstrual suppression, etc., up to a certain stage, by its exhibition. After the maximum effect had been obtained by relieving the insufficiency due to the secondary inactivity of other glands, then the pituitary treatment, which in these cases of bilobar involvement consists of giving both the anterior and posterior lobe substances by mouth and hypodermatically, was used, with additional good results of further alleviating the remaining obesity, constitutional symptoms, and other hormonic signs, which *had not been affected* by giving the simple products of other glands, such as the thyroid and the ovary. This plan of treatment not only should be more completely successful as to final results, but is also of great diagnostic aid in determining absolutely what other ductless glands are secondarily involved. In fact, the writers have used this plan more for the sake of confirming the suspected diagnosis of secondary glandular involvement, than for the primary therapeutic effect to be obtained.

The exact dosage of the pituitary products, either by mouth or hypodermatically, is still very much in doubt. The reason for this is the fact that in individual cases there is a very marked difference in the activity of the lobes of this gland. The glandular products so far probably vary a great deal in potency, which is another factor making the dosage difficult to measure. The writers' limited experience has demonstrated that the best measure for dosage and frequency of the treatment, particularly the hypodermic injections of these substances, is *the amount of reaction* obtained in each individual case and the *effect of the dose,* given at definite intervals, *upon the signs and symp-*

toms of the disease. It will be understood from this premise how variable the dosage and interval must be in different cases. Only the general principles which have been deduced from the writers' clinical experience can be given. **Anterior lobe extract,** given intramuscularly in 1 c.c. (minims xvi) doses, has never produced any perceptible reaction, febrile or otherwise. **Pituitrin,** or extract derived from the posterior lobe acid infundibulum of the hypophysis, does produce a very decided local *intestinal and general reaction.* The *general reaction* consists of marked tremor, blanching of the skin, general weakness, and nervousness in some cases, marked emotional disturbances, such as crying and depression. This *general reaction* has been noted after a dose of 0.12 to 0.5 gram (2 to 8 minims). It usually occurs within from three to five minutes following intramuscular injection. If the above dosage is given subcutaneously, the length of time before the reaction occurs is usually postponed to ten or fifteen minutes; and frequently the same dose given to the same individual, producing marked reaction intramuscularly, will not produce any reaction when given subcutaneously. The *local reaction upon the peristalsis of the intestine* usually occurs within two or three minutes after the injection. It consists of severe abdominal pains, described as "cramps," followed within a few minutes by a bowel movement. It has been the writers' custom to try to remain below the *general* reaction of the posterior lobe extract, and at the same time to give as large a dose as possible up to *the production of the local or intestinal reaction.* In some cases only 1 or 2 minims (0.06-0.12 c.c.) subcutaneously, and in other cases 60 minims (4 c.c.) intramuscularly, have been borne without reaction. The interval of dosage is first set at seven days; and if this is not productive of a satisfactory result, the interval is gradually decreased so that one, or sometimes two doses are given a day. It has been noted that in those cases under hospital observation, in which smaller doses are given daily, the results have been much more decided. In those cases in which even a total larger dose is given every five to seven days, results have not been so good as in those cases in which a small total dose has been given at daily intervals throughout the week. With this dose of posterior lobe, there is included in the bilobar cases 1 c.c. (minims xvi) of **anterior lobe extract hypodermatically** and **anterior lobe of pituitary,** grains ii ss - xv (0.16-0.972 gram) three times daily, after meals. In addition to this treatment, in those cases having a decided insufficiency of the ovaries, there are added **hypodermatic injections of corpora lutea** or **ovarian residue** (extract from the interstitial substance of the ovary). These ovarian extracts are not given as frequently as the pituitary extract.

It has been the writers' routine first to place *amenorrheic pituitary cases,* which can be kept under observation for a considerable length of time, upon corpora lutea, the treatment consisting of 1 c.c. (minims xvi) of corpora lutea and grains v to x (0.3-0.65 gram) of corpus luteum by mouth three times a day, over a considerable length of time. This is done to test out the independent effect of this substance upon the disturbances of the menses. If there is no decided result obtained from this, then they are given the ovarian residue (extract derived from the interstitial portion of the ovary) in doses of 1 c.c. (minims xvi) once or twice a week, or at even more frequent intervals, in order to determine its effect upon the amenorrheic signs. If neither of these substances of the ovary has any favorable effect upon the imperfect periods, **thyroid gland** is added, by mouth, in graded doses. If a combination of thyroid and ovarian substance has no beneficial effect, then **adrenalin** might be used in addition. In this way, all of the secondary glandular insufficiencies are determined, in so far as confirming the diagnosis, as well as the effect of the individual gland or combination of these substances upon the presenting hormonic signs. Treatment is given until amelioration of the symptoms occurs, causing them either to become stationary or to cease entirely. Then, last of all, **pituitary lobe extracts** are added, either singly or in combination, depending upon the outspoken hormonic signs indicating insufficiency of one or both lobes. If one of the individual lobes of the hypophysis is most decidedly affected, substance from this lobe is used alone. After a careful and prolonged observation of the use of other endocrinous glandular treatment, combined with extract from one lobe of the gland, has been carried out, the other lobe is substituted or used in addition to the one first given. The value of this plan of treatment will easily be seen, in advancing the knowledge, first, with regard to the diagnosis of the number of ductless glands involved, and second, with regard to the result which might be obtained from the single glandular therapy as compared with that of polyglandular treatment. The knowledge concerning the entire relationship of the ductless glands will undoubtedly be much more rapidly projected by a routine form of treatment of this kind carried out by many individuals whose different views of the subject as a whole will do much to check up and control the views of a single advocate, and consequently advance the general principles underlying the treatment of these dyscrasias.

It must be borne in mind that this medical treatment, consisting of the simple substitution of glandular products, is indicated only in those hyposecretory cases *not having pituitary neoplasm* or other intracranial pressure symptoms resulting from diseases of the pituitary gland. It is well known that a number of types of diseases of this gland, usually classified among the hypopituitarisms, which *do not have enlarged sella turcicæ* roentgenologically, do have evidence of intracranial pressure symptoms directed upon the hippocampal gyrus or the olfactory nerves. These are the cases associated with epileptiform attacks, with or without disturbances of the senses of taste and smell. In these cases of hyposecretions, one is justified in trying out a **glandular therapy**; but if this is not successful within a reasonable length of time (six or eight months), **surgical operation** in the form of trans-sphenoidal decompression should be considered. It is also to be borne in mind that only those hypophyseal diseases having *underactivity* of the function or secretion of the pituitary lobes are suitable for glandular treatment. Those cases of the opposite function, having an overactivity or hypersecretion, should, according to established theories, be made much worse by the exhibition of their glandular substances. The custom of giving additional pituitary gland to hypersecretory diseases of this gland, would be exactly like giving thyroid gland, iodin, or iodid to a case of hyperthyroidism. Those cases already having an excess of secretion from either lobe of the hypophysis, certainly ought not be given more of the extract of the individual lobe already producing such deleterious effects upon other organs and tissues of the body. This again emphasizes the need of the most discriminating diagnosis directed not only toward the pituitary gland as the cause for the patient's complaints and toward the lobe producing these disturbances, but also the *necessity of estimating the activity* of the secretion or the functional state *of each lobe,* in order to determine the kind of treatment indicated. Treatments of hyperactivities of one or both lobes have been taken up in detail in the sections dealing with this division of the subject. It might here be added in this regard, that the treatment directed against *overactivity* of either one or both lobes of this gland, consists of those agencies which decrease glandular activity or inhibit cellular growth. In those *hyperpituitarisms having neoplastic etiology,* early surgical treatment is indicated. In those having aneoplastic *hypersecretion,* **x-ray** and **radium**, which are said to be effective in depressing their overactivity, should be given a trial for a certain length of time. If these fail, and the progress of the disease becomes rapid, **surgical intervention** should be considered.

Local treatment directed toward any of the hormonic signs such as obesity, amenorrhea, constitutional disturbances, gastro-intestinal disorders, dyspnea, etc., has been found absolutely useless. **Symptomatic treatment** directed toward the headache, somnolence, and other constitutional symptoms, has certainly been very discouraging. Large doses of **sedatives** and **narcotics** are required to produce even slight effect, and no other treatment has been found valuable to prevent frequent recurrences of the same symptoms. However, it is true that many of the *hypersecretions* of the lobes of this gland, after a year or two, change into *hyposecretions,* necessarily producing the opposite manifestations in the hormonic signs, such as emaciation to obesity, polyuria to anuria, normal to aplastic genitalia, etc. This is not true in any large percentage of cases of primary hypopituitarism. The primary deficiencies of this lobe of the hypophysis rarely ever change into overactivity. The hypopituitarisms usually run a rather progressive, continuous course, with the constant addition of new and more distressing clinical manifestations. This progress is interrupted in some cases by **polyglandular therapy.** In those cases in which a favorable result is obtained by glandular treatment, this treatment should be continued for a prolonged period of time. After all the signs and symptoms have been definitely controlled, an attempt should be made to gradually reduce the treatment, with regard to both the dosage and the interval. The writers have found very few cases, however, in which a favorable result has been obtained, in which the treatment could be entirely stopped without a return of many of the original complaints and signs. The insufficiencies of this gland are very similar to those of the thyroid, and it is likely that very few of them ever return to their normal activity and function. Another reason why they should be observed indefinitely, is the fact that a certain percentage change into definite hyperplastic adenomas of the pituitary. When this change occurs, there is, as has been previously stated, definite indication for **radical surgical interference**, and this should be recommended before damage has been done to the surrounding structures of the brain.

Prognosis.—The prognosis of bilobar types has been given under the previous section describing pre-adolescent hypopituitarism of this variety. It is only necessary to add that up to the present time the prognosis has not been favorable in this variety of case. This is due to the fact that it is very difficult to determine in an individual case, of those not having neoplastic changes of the pituitary, just what reaction will occur to treatment. The effect of glandular treatment has not been sufficient in a large number of these cases to say definitely whether it can be relied upon to produce beneficial results. Added experience will probably work out a more rational treatment, based upon more accurate indications, and give hopes of better ultimate results. Those recent cases having partial or slight deficiency of both lobes, it would stand to reason, should react better than the more advanced decided insufficiencies which have existed for a long time. As compared with unilobar insufficiencies of the anterior lobe, the bilobar insufficiencies are much less favorable in every way. The anterior lobe controlling the skeletal growth and gonad function cannot produce such very decided serious effects upon the individual as a whole as those produced by the posterior lobe, whose secretion is so much more important, influencing many very necessary functions pertaining to metabolism and vital organs having to do with the normal life of the individual. Thus the prognosis of bilobar hypopituitarism depends upon the amount of restoration of function of the posterior lobe which can be established by treatment. If the insufficiency of this lobe is easily balanced by simple glandular substitution, the prognosis, at least with regard to relief of symptoms, is very good. The type of disease, that is, whether neoplastic or aneoplastic, is another factor which governs the prognosis to a large extent. The aneoplastic are undoubtedly much more favorable, with regard to both relief of symptoms and duration of life, than are the neoplastic. A great majority of the pituitary neoplasms are unfavorable from the point of view both of relief and of ultimate results. Even those who are operated upon early have marked tendency to recurrence, requiring numerous operations to control the symptoms, and even then, in the course of a few years, the cases may result unfavorably.

Pathology.—The pathology in these 3 cases with regard to the structural changes in the pituitary gland cannot be given. Only those minor changes in other endocrinous glands and those due to hormonic structural changes in other organs, can be surmised from the clinical signs. With regard to other ductless glands, it is likely that in 2 of these cases (XIV and XV) there was involvement of the thymus. There were no physical signs to substantiate such a statement; yet the dyspnea and substernal pressure would lead one to suspect possible involvement of this gland. It is also known that the thymus gland does not become atrophic unless there is complete activity of secretion of the gonads at the age of maturity. This was not present in either of these cases, as would be suspected from the long periods of amenorrhea present in both. The unusual development of the long bones might be attributed to the persistent thymus secretions and function, provided it could be proved that this was present in these cases. It is taken for granted that there was an insufficiency of the anterior lobe of this gland, which normally stimulates the growth of these bones. This overgrowth cannot be due indirectly to hypersecretions of the posterior lobe, as there were no other hormonic signs of such hypersecretions early in the course of these cases. Yet in both we have an unusual overgrowth of the long bones, as is shown by the measurements. Other glands which we know have to do with the growth of the bones, are the thyroid, and possibly the thymus. Whether this overgrowth is due to the thymus in conjunction with the thyroid, however, is absolutely speculative. It is merely mentioned here as a possible explanation for the long bone length. As stated under Treatment in this section, from the effects of treatment, insufficiencies of both the adrenals and the thyroid have been suspected. There was no definite clinical evidence to this effect, but the result of treatment, particularly in Case XIV, helps to prove such a supposition. The insufficiency of the gonads is a result of the anterior lobe insufficiency. It will be noted that the uterus, in Case XIV, and also probably in Case XV (although it could not be determined at examination), was well developed. This is due to the late onset and incompleteness of the insufficiency of the anterior lobe. This is more easily demonstrated in the male, where the effect of this secretion upon the genitalia is more objective. Those cases of anterior lobe insufficiency coming on late in life, *after* the gonads and penis have been developed, show little effect upon their size and development, although there is decided effect upon their functions. In some cases there are retrogressive changes in these organs, consisting of diminution in size, after the onset of the anterior lobe insufficiency. The mammary glands in both of these cases were very large, overgrown, and pendulous. The difference in the size of this gland, as compared with the pre-adolescent type, has been mentioned. This difference is probably also due to the time at which the inactivity occurs. In those cases developing after the mammary glands have been well developed and already changed to the pendulous type, it is unlikely that they undergo decided change, although there are some cases in this series in which the history is very positive for reduction in the size of these glands following pituitary insufficiency. The other pathological changes occurring in the organs and tissues are the ordinary ones present in the bones, adipose tissue, infiltrations, etc., due to insufficiency of both lobes of the pituitary. They have been described in previous chapters dealing with primary independent insufficiencies of each lobe of this gland, and also in the sections describing cases in which both lobes are involved.

SECTION 9

PITUITARY EPILEPSY

(Anterior and Bilobar Insufficiency, Postadolescent, Aneoplastic Types)

This section will be devoted to a group of pituitary cases in which the *presenting symptom is a type of epilepsy.* The 6 illustrative cases belong to the hyposecretion of the pituitary gland. Four of these cases are male, 3 of which are pure anterior lobe insufficiencies, 1 being probably a bilobar involvement. Two of these cases are female, both of which are bilobar insufficiencies of the hypophysis. One of the female cases has associated with it a mild, and the other, a decided secondary hypothyroidism. Three of these cases have been under the authors' observation, 1 for three years, and the other 2 for four months. The remaining 3 cases have been observed only a few days, for the purpose of diagnosis. Of the 3 cases under observation, 2 have been decidedly benefited by pituitary treatment.

Etiology.—Trauma was present in 2 of the following cases (XVII and XX). These occurred early in life many years before there was definite evidence of epilepsy. Both of these cases showed some retardation in skeletal growth, which would lead one to suspect that there was some insufficiency of the anterior lobe during the pre-adolescent life. In one case (XXI) the marked reduction of the secretion of the gland undoubtedly followed pregnancy, an etiological factor to which frequent reference has been made in previous sections. Nearly all of the cases had very severe early infectious diseases, but there is no definite relationship between any of these diseases and the onset of the pituitary dyscrasia. In 2 cases there is a family history of pituitary disease. In Case XVII there is a distinct pituitary family, in which the father and a number of brothers and sisters are typical pituitary types of individuals. Cases XVIII and XXI are brother and sister, but there is no other familial history. It is interesting to note that these 2 patients are practically of the same size with regard to skeletal growth. The sister, however, has evidence of posterior lobe insufficiency, which is entirely absent in the brother.

Symptomatology.—HISTORY: CASE XVII.—Mr. P. C., aged twenty, St. John's Hospital, General No. 1658, June 30, 1914. (*Anterior Lobe Insufficiency.*)

Present.—Chief Complaints: (1) *Epileptiform attacks;* (2) ***constipation,*** associated with occasional evacuation of a ***large amount of mucus.***

Duration.—One year.

Course.—(*a*) *Onset* was sudden. The patient had always been perfectly healthy up to one year ago, when he was suddenly seized with an attack of "unconsciousness and convulsions." This came on in the evening and lasted for only a short time.

(*b*) *Progress:* During the past year the patient has had four similar attacks. All occurred late in the afternoon or in the evening, but none during sleep. The patient has no focal or localized aura, none referable to the special senses. His aura consists of general uneasiness, a feeling as if he were pursued or falling off a precipice. This is soon followed by complete unconsciousness, during which the patient has first clonic, then tonic contractures, with frothing of the mouth, biting of the tongue, labored respiration, and cyanosis, followed by pallor. Some attacks have been preceded by drowsiness, with lack of concentration. The convulsion is followed by prolonged sleep, after which the patient awakens without depression or any other untoward after effects. The constipation has been a chronic complaint of longer duration than the epileptic attacks. The patient is of the opinion that when the constipation is severe and there is failure of bowel movement for two or three days, an attack follows. He also notices that he is more somnolent during his constipated periods. At this time he feels "dopy" and is unable to read or concentrate his mind. During the five months' treatment following the onset of his trouble, when an enema was used daily, no epileptiform attacks occurred.

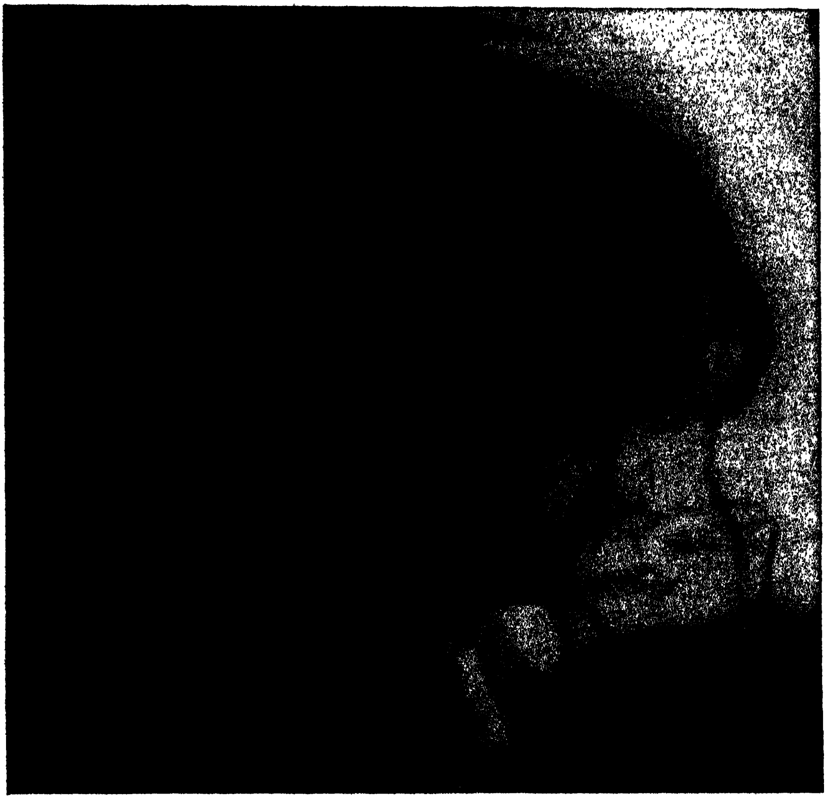
Past.—Diphtheria in childhood. Was struck on the head with a lead pipe when six years of age; scalp wound following this injury became infected, requiring treatment for a year.

Personal.—Moderate use of tea and coffee. Habits regular, sleeps well. Constipation for years. Venereal history negative. The patient uses alcohol and tobacco very occasionally.

Family.—Mother is a hypothyroid type. Father, one brother, and two sisters have definite signs of acromegaly. One brother is a eunuchoid type. Epilepsy and other nervous diseases negative.

EXAMINATION.—*General.*—Young man about 5 feet 4 inches tall, weighing 132 pounds. Muscular development marked. Lateral diameter of the head nearly equals the anterior-posterior diameter. Head covered with rather coarse dark hair, with the exception of a small area on the vertex just posterior to the posterior fontanel. This area is completely devoid of hair, due to an old injury. Hairline low, temporal hairline almost meeting the outer line of the eyebrow. Eyebrows meet in the median line. Eyes rather deep-set, far apart. Nose prominent, not pointed or blunted. Upper teeth not separated, lower teeth distinctly crowded. Hair sparsely covering anterior chest, somewhat abundant posteriorly. No abnormal distribution of hair about the abdomen, normal distribution on the extremities. Body of hands and feet large, although phalanges are short and wide. Few chloasma spots about the outer margins of the eyes. No abnormal gait, station, or position. Pulse, slow, equal in volume and tension. Temperament psychoneurotic, well controlled.

Regional (Positive Physical Signs).—*Head,* of moderate size, typically pituitary in form. *Nose,* straight. *Eyes,* deep-set. *Chin,* rather prominent, no prognathism. *Mouth:* No separation of the upper incisors, overcrowding of the lower. *Face:* Very slight chloasma over the malar prominences. *Neck,* negative. *Lungs, pleuræ, heart,* and *vessels,* negative. *Abdomen* and viscera negative. *Genitalia,* well developed. *Extremities* and *reflexes,* negative.



CASE XVII. FIG. 1.—NOTE VERY SMALL SELLA TURCICA, WITH PARTIAL APPROXIMATION OF ANTERIOR AND POSTERIOR CLINOID PROCESSES.

LABORATORY FINDINGS.—*Urine.*—Fourteen twenty-four-hour specimens. Albumin faint trace, indican considerable amount, skatol negative. Specific gravity 1.022, reaction acid. Dextrose, casts, erythrocytes, and leukocytes negative.

Feces.—Fourteen specimens (following blood-free diet). Four specimens showed a considerable amount of mucus, in long shreds or homogeneous masses. Blood, leukocytes, ova, and the parasites were negative.

Blood:	
Erythrocytes	5,000,000
Leukocytes	9,200
Sugar Tolerance Test:	
Blood-sugar	0.071
Blood-sugar (two hours later, after ingestion of 106 grams (3¾ ounces) dextrose by mouth)	0.078

SPECIAL EXAMINATIONS.—*Fluoroscopic.*—No six-hour gastric residue. Gastric tone and motility good; no filling defect, incisura, niche, or bud. Duodenal cap large, well formed, margins free from defects. Second portion of the duodenum visualized. Six-hour meal in the cecum and the right half of the transverse colon.

Roentgenogram of Head.—Sella turcica small. No other abnormal markings.

HISTORY: CASE XVIII.—Mr. W. F. R., aged twenty-three, St. John's Hospital, General No. 1696, April 9, 1918. (*Anterior Lobe Insufficiency.* Brother of Case XXI.)

Present.—Chief Complaints: (1) *Epileptiform seizures, preceded by aural aura;* (2) occasional feeling of *distress and discomfort in the epigastrium,* accompanied by bloating and distention; (3) attacks of *constipation,* no mucus in the stool.

Duration.—Four years.

Course.—(*a*) *Onset:* Until the onset of the trouble four years ago, the patient had been in good health; no history of convulsions or spasms, head injuries, etc. At the time of the onset, while at the table eating, he noticed a ringing in the ears, which gradually became worse. The patient rose from the chair, started to walk, and *fell unconscious to the floor.* This attack lasted probably between five and ten minutes. After regaining consciousness, he felt weak and somewhat numb. During the attacks, the patient has tonic convulsions, frothing at the mouth, and at times has bitten his tongue.

(*b*) *Progress.*—During the past four years the patient has had several attacks, at intervals varying from about seven weeks to sixteen months. During this time he has taken different kinds of treatment, without relief. However, he is of the opinion that the attacks are lighter at present. The patient is able to associate the attacks with the taking of alcoholics, extreme exercise, cold showers, or staying up late at night. During the sixteen-month interval of freedom from attacks, he abstained from all liquors, exercise, and all excesses. The attacks are preceded by an aura, in which the patient notices buzzing in the ears. This becomes more marked, and is followed by a rush of blood to the head and blackness before the eyes, when the patient falls unconscious. During the unconscious period, he is told that he has tonic contractures of the muscles, shaking, and frothing at the mouth, and he occasionally bites his tongue. Since these attacks began, the patient has not noticed any disturbance in memory, attention, or concentration. No visual disturbances or perversion of taste, smell, or other special sense, except hearing. At times preceding attacks he hears voices, which are not present, "usually his mother's voice." At times he has hallucinations and illusions before the attack. The patient is also subject to a feeling of distress and discomfort in the epigastrium, associated with distention and bloating, and with chronic constipation. Bowel movement relieves this condition in the epigastrium. No history of mucus in the stool. No symptoms referable to other systems.

Past.—Mumps, whooping cough, frequent sore throat, no rheumatism. No operations. One injury, fracture of wrist two years ago.

Personal.—Patient single. Appetite good, bowels constipated, no disturbance of urination. Is restless at night when constipated, otherwise sleeps well. Does not use coffee or tea, alcohol moderately (at intervals none at all). No venereal disease.

Family.—Father dead; mother living, well. Two sisters, two brothers living. One brother and one sister dead. No family history of cancer, tuberculosis, epilepsy, etc. One sister has a goiter. One sister is under personal observation for pituitary epilepsy (Case XXI).

EXAMINATION.—*General.*—Acromegalic type of individual, with classical hands, projection of the lower jaw, typical nose, large head, and deep-set eyes. Genitalia show normal development. No marked pigmentation about the body, except slight chloasma about the face. Pulse, slow, low volume and tension, equal, symmetrical, rate exceedingly slow, rhythm good, no special type. Blood-pressure, systolic 120, diastolic 70. Temperature, 97.6°-99° F. (36.4°-37.2° C.). Pulse, 60-80. Respiration, 18-26. Measurements: Height, 5 feet 5½ inches (166 cm.); length of humerus, 13 inches (33 cm.); forearm, 10 inches (25 cm.); femur, 18 inches (41 cm.); lower leg, 17½ inches (44 cm.); circumference of head, 23½ inches (60 cm.); neck, 14½ inches (37 cm.); chest, 35½ inches (90 cm.); at navel, 32½ inches (83 cm.); hips, 34½ inches (88 cm.). Weight, 150 pounds.

Regional (Positive Physical Signs).—*Head:* Hair very thick, coarse; slight chloasma about the forehead; eyebrows meet over the nose. *Eyes:* Deep-set. *Mouth:* No loss of dentine in the teeth, marked separation of the upper incisors, no overcrowding of the lower anterior teeth, only four posterior molars have been slightly treated. *Neck:* Thyroid gland slightly full, no definite enlargement or vascularity; marked pulsations in both the carotids and jugulars, pulsation of the latter not positive. *Abdomen* and visceral organs negative. *Genitalia:* Testicles and penis normal.

LABORATORY FINDINGS.—*Urine.*—(*a*) Single specimen, pale, specific gravity 1.012, alkaline in reaction. Trace albumin. Dextrose, erythrocytes, leukocytes, and casts negative.

(*b*) Twenty-four-hour specimen, 2,000 c.c., pale, specific gravity 1.010, reaction acid. Trace albumin, occasional leukocyte. Dextrose, erythrocytes, and casts negative.

(*c*) Twenty-four-hour specimen, 1,500 c.c., pale, reaction acid, specific gravity 1.011. Trace albumin. Dextrose, erythrocytes, leukocytes, and casts negative.

Feces.—Three specimens, following blood-free diet, brown, formed. Mucus, pus, ova, and parasites negative. Occult blood positive (one specimen).

Blood:

Erythrocytes	5,340,000
Leukocytes	10,000
Hemoglobin	105 per cent.
Wassermann	negative
Stained smear	normal

Sugar Tolerance Test:

(*a*) Blood-sugar	0.086
(*b*) (Following 400 grams (14 ounces) glucose, given in twenty-four-hour diet, and injection of adrenalin 1/1000)	0.062

Special Examinations.—*Roentgenogram of Head.*—Nasal bone unusually well developed, frontal sinus large, sphenoid small. Sella turcica 12 x 15 mm. (normal). Aural canals and mastoid cells clearly differentiated. No projection of the lower jaw, teeth negative.

Trochoscopic.—Rectal pouch spastic, very narrow. Pelvic and iliac colon spastic. Splenic flexure wide; transverse colon not dilated, large, not mobile. Ileocecal valve incompetency.

Anterior Pituitary Extract Reaction.—1 c.c. at 12:30 p. m.

Time	Temperature
1:00 p. m.	98° F. (36.7° C.)
3:00	98.4° F. (36.9° C.)
5:00	99° F. (37.2° C.)
7:00	98.6° F. (37° C.)
	(Subnormal entire following day)

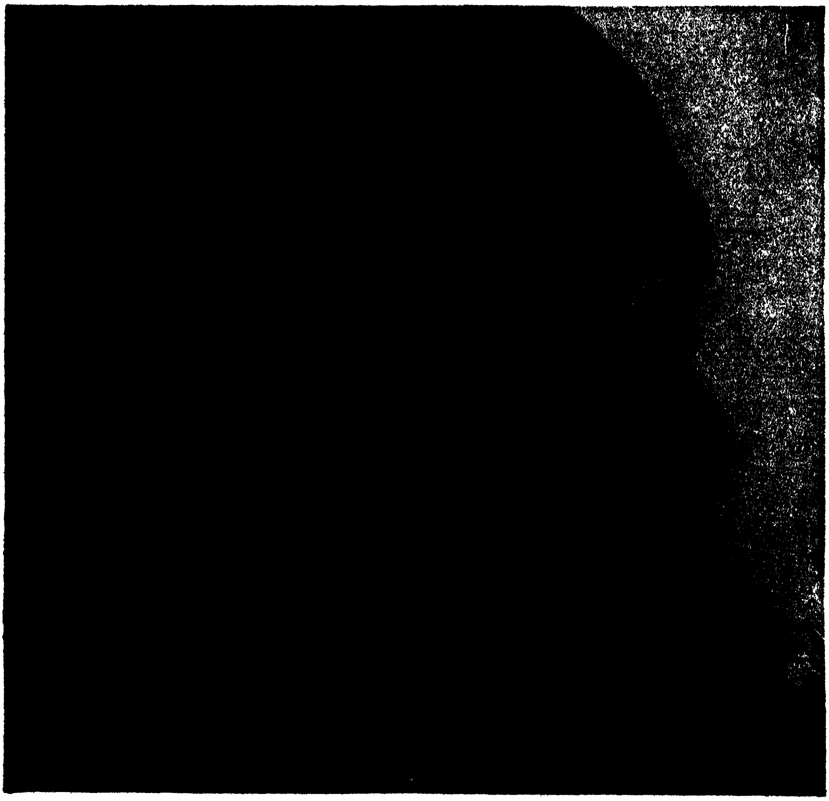
History.—Case XIX.—Mr. W. O'H., aged thirty-five, St. John's Hospital, General No. 633, December 10, 1917, referred by Drs. LaRue and LaRue, Dexter, Mo. (*Bilobar Insufficiency.*)

Present.—Chief Complaints: (1) *Spells of mental clouding, haziness, and semiconsciousness,* usually preceded by nausea, or a sensation described as "catching in the stomach," which is followed immediately by the attack. No complete loss of consciousness, visual disturbance, headache, convulsions, tremor, or other nervous manifestations. (2) *Sudden impotence* since the onset of the above attacks.

Duration.—Six months.

Course.—(*a*) *Onset.*—The first attack occurred six months ago, during the night, following a day in which the patient had indulged heavily in "sweet stuffs." He had been somewhat nauseated during the night, but did not vomit. No other manifestations. The patient was awakened by the attack, which came on suddenly as a mental clouding and haziness. No complete loss of consciousness, no muscular quivers, convulsions, nor incontinence. No visual disturbance nor other accompanying symptoms. Duration, from one-quarter to one minute.

(*b*) *Progress.*—On the next day the patient had a similar attack; in the past six months attacks have been occurring as frequently as three times a day, with occasional intervals of freedom as long as a week.



CASE XVIII. FIG. 1.—SELLA TURCICA MEASURES 12 x 15 mm (normal).

There is usually an indefinite aura, in that the patient feels slightly nauseated, or has a "catching" or "striking" in the stomach, immediately preceding the attack. The patient is not incapacitated at any time, is able to hold a conversation and retain the line of argument, and is able to walk, think, and carry on the ordinary physical and mental activities. The only difficulty experienced occurs after the attack is over, when he is unable to recall distinctly, without haziness, what transpired during the attack, although there is some indefinite recollection. The attacks occur at no particular time: occasionally during the night, at times during the day, and even during eating, at which time the patient continues to eat. The attack, as mentioned, lasts not longer than a minute, and its disappearance *is accompanied by a disagreeable taste.* There are no signs or symptoms referable to other systems—no diplopias, urinary hesitancy, paresthesias, disturbance of gait or station, etc. No headaches, disturbances of vision, changes in the hands or feet, or loss of hair. There has been a rapid gain in weight. At the age of twenty-four the patient weighed 130 pounds, and in the succeeding two years his weight reached 175 pounds, without other manifestations. There has been marked loss of libido since the onset of the attacks of epilepsy. Previous to that time the libido had been hypersexual.

Past.—Measles, mumps, muscular rheumatism (cramping at night).

Personal.—Coffee moderately, alcohol very moderately, no tobacco for the past six years. Gonorrhea fifteen years ago; no specific history. Appetite good, sleeping variable (patient states that either attacks prevent sleeping or loss of sleep brings on the attacks). Bowels regular. Patient married. Has five children, well; one child died in infancy. Wife has had no miscarriages. Impotence occurred with the onset of epilepsy. Patient's infancy was healthy, no tendency to convulsions, spasms, etc.

Family.—Father died, aged sixty-six, apoplexy. Mother living, aged sixty, well. Two brothers dead, one of "congestion of the stomach" at the age of twelve, one of pneumonia at the age of eleven. Five sisters living, well. No family history of tuberculosis, cancer, or other hereditary diseases. No history of nervous manifestations, as epilepsy.

EXAMINATION.—*General.*—Exceedingly well-nourished man, with tendency to obesity, which is not particularly localized. Height, 5 feet 5 inches; weight, 185 pounds. Very marked abnormal distribution of hair: hair very heavy about the nipples and along the sternum, diffusely present over the abdomen, particularly in the epigastric region; hair on the extremities excessive, on the extensor sides of the forearms and on the legs; that on the mons does not stop at the level of the symphysis. Hair of the face, eyebrows, and eyelids also, thickly distributed. No abnormal pigmentation, skin lesions, or scars, except a few indifferent ones around the base of the sacrum, and on the anterior surfaces of the tibiæ, scars not decidedly pigmented. Color good: nails well colored, skin of a normal pink. *Hands and feet small.* (Size of glove, No. 8, fingers too long. Size of shoe, No. 6½.) Pituitary type of individual in proportions, yet no marked girdle obesity. Some obesity about the chest, mammary region, and the neck; no thyroid obesity in supraclavicular spaces, or about the posterior neck. Long bones not developed, flat and short bones rather fragile, except those of the head. Pulse, slow, regular, equal, symmetrical, low volume and tension, rhythm good, no special type. Temperature 97.4°-98.8° F. (36.3°-37.1° C.); pulse, 64-88; respiration, 20-24. Blood-pressure, systolic 150, diastolic 80.

Regional.—Head: Oval face, thyroid type, somewhat triangular in shape, forehead narrow, head through occipital region rather broad. Skull, scalp, sinuses, fontanels, all normal; no anterior-posterior or lateral compression symptoms, slight localized tenderness over the supraorbital nerves and frontal sinuses, none in the temporal regions, over muscle insertions, mastoids, occipital nerves, vertex, or cervical region. Percussion note practically equal, bilaterally. *Mouth:* Lips crusted, dry; anterior teeth worn decidedly, definite separation of the two central incisors above, other teeth well preserved. Mucous membranes slightly injected, tongue coated posteriorly, tonsils very much enlarged, irregular, and injected, pharynx red and injected. *Chest:* Negative. *Abdomen* and visceral organs negative. *Genitalia:* Penis rather small, testicles well developed; no scars or other abnormalities.

LABORATORY FINDINGS.—*Urine.*—(*a*) Single specimen, color straw, specific gravity 1.015, reaction acid. Dextrose, casts, and erythrocytes negative. Leukocytes 3 to high power field, faint trace albumin.

(*b*) Twenty-four-hour specimen, 1,620 c.c., pale, specific gravity 1.010, reaction acid. Dextrose, casts, leukocytes, and erythrocytes negative. Faint trace albumin.

(*c*) Twenty-four-hour specimen, 720 c.c., color straw, specific gravity 1.020, reaction acid. Dextrose, casts, and erythrocytes negative. Occasional leukocyte, faint trace albumin. Calcium oxalate crystals present.

Feces.—(*a*) Following blood-free diet, brown, formed. Mucus, pus, ova, parasites, and occult blood negative.

(*b*) Whitish, formed. Mucus, pus, ova, parasites, and occult blood negative.

Blood:

Erythrocytes	5,500,000
Leukocytes	10,200
Hemoglobin	110 per cent.
Wassermann	negative
Stained smear	normal

Blood-sugar:

(*a*) First specimen	0.080
(*b*) (Following the ingestion of 400 grams (14 ounces) glucose in twenty-four hours, and adrenalin 1/1000, m. x. 'H')	0.108

Spinal Fluid:

Wassermann	negative
Globulin	negative
White-cell count	0

Stomach Content.—Ewald test meal, one hour in stomach, well chymified. Free hydrochloric acid 20, total acidity 30. Lactic acid, mucus, and bacilli negative.

SPECIAL EXAMINATION.—*Fluoroscopic.*—*Head, neck, lungs, heart, mediastinum, diaphragm,* and *stomach* negative.

Roentgenogram of Head.—Head rather small in size, normal thickness of the skull. Sinuses free from shadows. *Sella turcica very small,* anterior and posterior clinoid processes only about one millimeter apart.

Mastoid cells negative, no shadow over the pineal gland. No evidence of differences in thickness of the skull, or other evidence of intracranial pressure. Teeth free from infection along the roots.

Trochoscopic.—Negative.

SUBSEQUENT COURSE (June 14, 1918).—Since leaving the hospital the patient has been under the following treatment: **Anterior lobe pituitary gland,** grains v (0.3 gram) has been given after meals (three times daily), **anterior lobe extract,** minims xvi (1 c.c.), hypodermatically every three or four days. During the two months of this treatment there has been no change in the severity or frequency of the attacks of petit or grand mal. Following this, beginning two months ago, the anterior lobe treatment was discontinued and **posterior lobe (pituitrin),** minims xvi (1 c.c.), given every three days intramuscularly. The following reaction occurred after the injection of the pituitrin. Within five minutes the patient noticed pain in the occipital region, which extended upward toward the vertex of the skull and finally located in the right parietal region. This pain was accompanied by tenderness, which remained during the three-day-interval between the injections. Besides the simple posterior lobe pituitary treatment, symptomatic treatment, such as **cathartics** for constipation, was given. During the last month **sodium bromid,** grains xv (0.972 gram), after meals, has been added. The patient states that since the institution of posterior lobe treatment attacks have been less frequent and less severe. Instead of occurring daily, they have occurred only once a week during quiet and rest at home. While the patient was traveling, they occurred not oftener than every other day. Many of them were so mild that there was only slight nausea, without other evidence of attacks, such as slight loss of consciousness, confusion of ideas, or grand mal attacks. The gustatory symptoms, which were constantly present following the attacks before the pituitrin treatment, have disappeared entirely. There has been some disturbance of gait. The patient feels clumsy, and has been told by friends that he limps when walking. No definite vertigo or ataxia is present at the time of examination. The patient has pains in the thighs and calves of the legs, associated with exhaustion, after prolonged effort such as walking for a distance. No change has been noted in the libido. The appetite is good, but not ravenous.

REËXAMINATION.—*General.*—No definite changes since the previous examination on December 10, 1917. Measurements: From head to symphysis, 32 inches (81 cm.); from symphysis to feet, 33 inches (84 cm.); length of humerus, 12 inches (30 cm.); forearm, 10 inches (25 cm.); femur, 16 inches (41 cm.); leg, 15½ inches (39 cm.); circumference of head, 22 inches (56 cm.); bust, 37 inches (94 cm.); navel, 38 inches (97 cm.); hips, 37 inches (94 cm.).

Regional.—Condition is practically the same as on the previous entrance.

LABORATORY FINDINGS.—*Urine.*—Single specimen, color straw, reaction acid, specific gravity 1.010. Dextrose, albumin, and microscopic negative.

HISTORY.—CASE XX.—Mr. M. H. W., farmer, aged twenty-seven, St. John's Hospital, General No. 2104, referred by Dr. E. A. Stierberger, Union, Mo., May 21, 1918. (*Anterior Lobe Insufficiency.*)

Present.—Chief Complaints: (1) *Epileptiform attacks;* (2) *frequent attacks of headache,* frontal and occipital type; (3) some *blurring of vision,* objects at times appearing to fuse, diplopia at times; (4) some *olfactory* and *gustatory disturbances;* (5) rattling sensation in the chest; (6) at times *heaviness over the precordia;* (7) at times loss of function of the left arm; (8) weakness in the lower extremities; (9) some *loss of weight, 15 pounds in the past three or four years.*

Duration.—Thirteen years.

Course.—(*a*) *Onset:* Sudden. Previous to the time of the onset thirteen years ago, there had been no history of similar attacks. The first attack came on immediately after the patient had been burned on the head with steam. However, the burn in itself was not sufficiently severe to cause any unconsciousness. Immediately following this the patient developed an epileptiform attack, without evidence of aura. This attack lasted fifteen or twenty minutes, during which time the patient lost all consciousness. No history of tongue biting, frothing at the mouth, etc. Consciousness gradually returned, followed by nervousness and drowsiness.

(*b*) *Progress.*—Following this other attacks occurred about every month; they were similar in character, but gradually increased in severity. The condition continued in like manner for about four years. At that time the patient quit school, and for the next five years had an occasional seizure, but these were less frequent and severe. The patient then began work in an office, and the attacks became more frequent and increased in severity. During the past four or five months they have been more severe, occurring about once a month. They are not of longer duration than formerly, but after the patient starts to regain consciousness, he does not know what he is doing for half a day, seeming to walk about in an extremely drowsy state, very inactive, unable to concentrate, and inattentive, able to talk, but without knowing what he is saying. He does not give a history of distinct aura, but the unconsciousness is commonly preceded by a state in which the patient walks about staggering, semiconscious, subsequently falling to the floor unconscious. This state lasts about fifteen minutes, and is succeeded by the semiconscious condition described above. As far back as he can remember, he has noticed at times *a peculiar odor,* of substances which were not present to the patient's knowledge; also a *peculiar gustatory sensation.* In the past five years he has had a numbness in the left arm, with some loss of function, the aid of the right arm being required to move this member. This condition does not seem to be associated with the attacks described above, occurring more commonly in the morning, worse when the weather is cold. Within the past three or four years the patient has lost about 15 pounds of weight. He occasionally suffers from a heaviness over the precordia. No expectoration, blood-tinged sputum, etc. For the past five years he has also been subject to frontal and occipital headaches, not constant, but occurring as often as every other day. These tend to come on after stooping or lifting. For the past three years there has been *disturbance of vision,* in the form of *blurring* and weakness, at times *diplopia,* not present following the epileptiform attack. No symptoms referable to other systems.

Past.—Measles, mumps, chicken-pox, whooping-cough, occasional tonsillitis. No operations. History of injury at the time the patient began to walk, when he fell about fifteen feet. He does not know whether or not he was unconscious, but fractured his skull, over the right supraorbital ridge.

Personal.—Patient married; has no children. Appetite fair, bowels regular, sleeps well, no disturbance of urination. Tea and coffee moderately, alcohol moderately. Denies history of venereal disease.

Family.—Father and mother living, well. Five brothers, four sisters living, well. No family history of hereditary diseases.

EXAMINATION: *General.*—Short, stocky, muscular man, twenty-seven years of age, with typical short, pudgy hands and feet. Great toes apparently overdeveloped, ends of toes flat. Typical pituitary head and face, well proportioned; nose prominent, straight, angular, chin angular, with prognathism. Slight fullness of the thyroid. Separation of the upper incisors, overcrowding of the lower teeth. No abnormal obesity. No abnormal distribution of hair, except slight amount above the symphysis. No abnormal pigmentation except very slight amount below the angles of the jaw. No edema, cyanosis, or dyspnea. No abnormal gait, station, or position. Pulse, slow, regular, equal, symmetrical, low volume and tension, no special type. Temperament psychoneurotic, well controlled. Weight, 143¼ pounds. Measurements: Height, 5 feet 6 inches (168 cm.); *from vertex to symphysis, 33 inches* (84 cm.); *from symphysis to soles of feet, 33 inches* (84 cm.); length of humerus, 11 inches (28 cm.); forearm, 10 inches (25 cm.); femur, 15½ inches (39 cm.); lower leg, 15½ inches (39 cm.); circumference of head, 21 inches (53 cm.); neck, 14¾ inches (37 cm.); chest, 34½ inches (88 cm.); abdomen, 26¼ inches (67 cm.); hips, 34½ inches (88 cm.). Blood-pressure, systolic 125, diastolic 88. Temperature, 97.4°-98.8° F. (36.3°-37.1° C.) (three days' observation). One temperature of 99° F. (37.2° C.) (on admittance to the hospital).

Regional.—*Head, ears, eyes,* negative. *Mouth:* Separation of the upper teeth. *Neck:* Thyroid slightly enlarged, both lobes. *Chest, abdomen:* Visceral organs negative. *Genitalia:* One undescended testicle, other of normal size.

LABORATORY FINDINGS.—*Urine.*—(*a*) Single specimen, pale, specific gravity 1.010, reaction alkaline. Dextrose, albumin, leukocytes, erythrocytes, and casts negative.

(*b*) Twenty-four-hour specimen, 2,000 c.c., color straw, reaction acid, Dextrose, albumin, leukocytes, erythrocytes, and casts negative.

(*c*) Twenty-four-hour specimen, 2,350 c.c., color straw, specific gravity 1.010, reaction acid. Albumin, dextrose, leukocytes, erythrocytes, and casts negative.

Feces.—Brown, formed, mucus, pus, ova, and parasites negative. Occult blood positive, two plus. (Two specimens.)

Blood:

Erythrocytes	5,030,000
Leukocytes	5,600
Hemoglobin	108 per cent.
Wassermann	negative
Stained smear	normal

Spinal Fluid:

Wassermann	positive, two plus
Globulin	faintly positive
White-cell count	0

Sugar Tolerance Test:

(5-23-18.) Blood-sugar	0.070
After taking 200 grams (7 ounces) dextrose by mouth in twenty-four hours	0.096
(5-25-18.) Blood-sugar (following fourteen-hour fast)	0.090
Two hours after ingestion of 105.8 grams (3¾ ounces) of dextrose	0.094

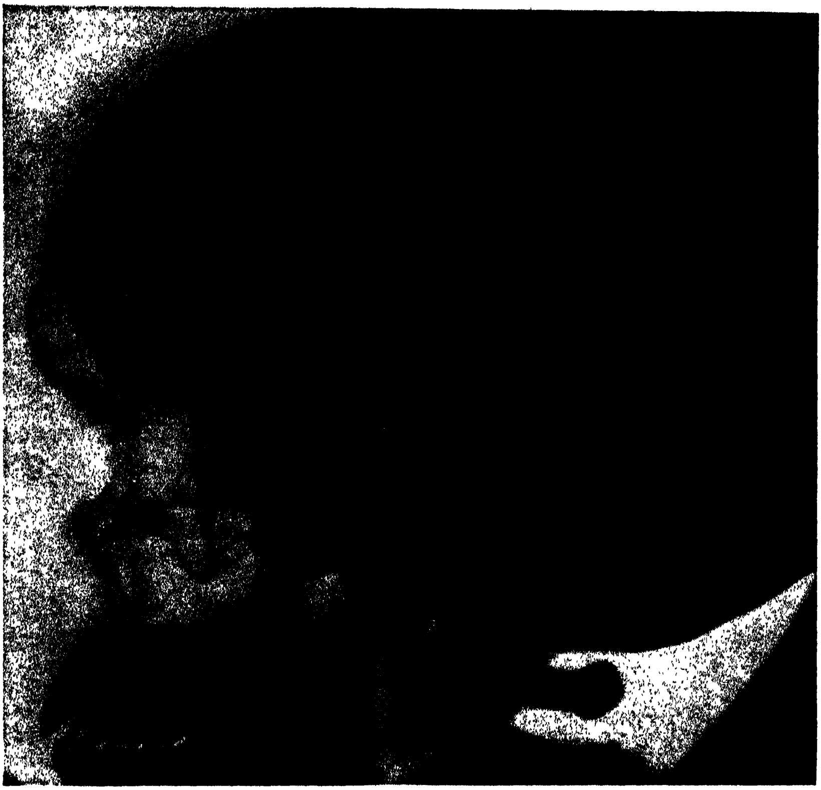
SPECIAL EXAMINATIONS.—*Roentgenogram of Skull.*—Sella turcica *normal in size,* posterior clinoid process sharply defined. Posterior meningeal artery markings decided. Frontal sinus large.

HISTORY.—CASE XXI.—Mrs. F. S., aged thirty-five, St. John's Hospital, General No. 1253, February 21, 1918. (*Bilobar Involvement, Associated with Hypothyroidism.*)

Present.—Chief Complaints: (1) *Epileptiform attacks.* During the attack the patient loses consciousness and does not respond to external stimuli. On recovery, she notices a sensation of a mass in the throat, feeling of suffocation, cardiac palpitation, numbness of the entire body, and stiffness of the hands and feet. The attacks last about one hour, followed by extreme weakness and somnolence, which persist for two or three days. (2) *Headaches,* in the left temporal and left occipital regions, accompanied by disturbance in vision, but no gastric trouble. (3) *Attacks of indigestion.* (4) Rather severe aching *pain in the small of the back,* coming on at irregular intervals, in attacks. (5) *Pain in the right hypochondrium.* (6) Marked *gain in weight;* 30 pounds within one year. (7) *Puffiness of the hands* (when the patient is unable to remove the ring from the finger), also *of the feet,* transient in character. (8) *Scanty periods* since the gain in weight. (9) Burning sensation following urination. (10) Attacks of *substernal weight and pressure,* accompanied by *transient dyspnea.*

Duration.—Two months.

Course.—(*a*) *Onset:* Very sudden. The patient was at a gymnasium ready to take exercise, when she was suddenly seized with an attack in which she lost consciousness, lasting for about one and one-half hours. Previous to this attack she had been complaining of severe headaches and the appearance of black spots and haziness before the eyes. After regaining consciousness, she noticed a "lump" in the throat, a feeling of suffocation, dyspnea, numbness of the entire body, palpitation, stiffness of the hands and feet, and twitching of the muscles of the arms and lower extremities. After this attack the patient felt extremely weak and nervous and was forced to go to bed. That same evening she suffered a similar attack, which was much milder, without loss of consciousness. The patient knew what was transpiring about her, but she did not seem able to react to stimuli. In both attacks she had a choking sensation, and was unable to swallow. The patient states that she knew when the latter attack was coming on by an aura of numbness of the body. During the attack, after the numbness had increased, her hands were immersed in very warm water, without her knowledge of it. This attack was much milder than the first, and of shorter duration.



CASE XX. FIG. 1.—NOTE NORMAL SELLA TURCICA.

(*b*) *Progress.*—Until two weeks ago the patient had been absolutely free from further attacks, but has been very nervous, at times irritable, subject to emotional states, crying without cause. Two weeks ago she was taken with a similar attack, which was much milder, also followed by extreme weakness. The fourth attack occurred one week ago. Since that time there has been freedom from distinct seizures, but there has been a sensation of numbness over the entire body. The patient has become extremely nervous, irritable, and emotional. She has been subject to general weakness, without loss of weight. Some disturbance in memory, and inability to concentrate as before. No history of tongue biting during the attacks. The patient has also suffered from *pain in the right side of the abdomen,* at times dull, at other times sharp in character, purely localized, not associated with bowel movement or with urination. Pain at the time of the onset has never been diffuse, and has never been accompanied by fever or chills; never sufficiently severe to require a hypodermic for relief. This pain has been present indefinitely, occurring in attacks, never sufficiently acute to require medical attention. During the year following the birth of her child (four years ago), the patient *gained weight very rapidly* (about 30 pounds.) The obesity seemed to be generalized, without tendency to any special type. She has also noticed *thinning of the hair,* no changes in pigmentation about the face, some *puffiness of the hands and feet,* tendency to moistness of the hands, and *scantiness of the periods.* No history of bruising easily, or of tenderness throughout the body. The patient is subject to *headaches,* usually in the *left temporal and left occipital regions, accompanied by some disturbance in vision,* but no gastric symptoms. These headaches usually precede the attacks described above. No signs or symptoms referable to other systems.

Past.—Measles, mumps, chicken-pox, whooping-cough, diphtheria, frequent attacks of sore throat; rheumatism. No operations or injuries.

Personal.—Coffee, but no alcohol. Patient is married, has one child, four years of age. No other pregnancies. Periods began at the age of fourteen, regular, lasting four or five days. *Since the birth of her child, periods have been scanty, lasting from two to three days, with some pain*—but no severe dysmenorrhea—preceded by headache. Appetite variable, sleep disturbed by restlessness, bowels regular, occasional pain following urination.

Family.—Father dead, apoplexy. Mother living, well. Several brothers and sisters living, well. Those not living died in infancy. No family history of hereditary diseases. One brother (Case XVIII) is under personal observation for pituitary epilepsy.

EXAMINATION.—*General.*—Unusually well developed, obese individual, 5 feet 3 inches in height, weighing 155 pounds. Pulse, slow, regular, low volume and tension, equal, symmetrical. *Marked girdle obesity,* from the navel to the midportion of the thigh. Breasts not unusually large. Marked supraclavicular fat pads. No obesity of the arms, hands rather free from fat pads. Forearms, hands, and feet unusually small; fat in the arms seems to stop at the midportions of the forearms. Long bones fairly well developed; flat bones also unusually developed, except those of the hands and feet. Bridge of the nose straight, tip pointed, chin sharp. No abnormal pigmentation, no abnormal distribution of hair. Highly psychoneurotic. Temperature, 97.6°-98.6° F. (36.4°-37° C.); pulse, 72-84; respiration, 20-24. Measurements: Height, 5 feet 3 inches (160 cm.); circumference of head, 20¾ inches (53 cm.); neck, 13 inches (33 cm.); bust, 34½ inches (87 cm.); waist, 29 inches (74 cm.); hips, 38½ inches (98 cm.); length of humerus, 12 inches (30 cm.); forearm, 9½ inches (24 cm.).

Regional (Positive Physical Signs).—*Head:* Anterior-posterior diameter increased. *Mouth:* Teeth very straight, upper incisors separated, no overlapping or crowding of the lower anterior teeth; considerable number of teeth missing, those present show decay. *Neck:* Supraclavicular fat pads present bilaterally, none over upper thoracic vertebræ. No enlargement of the thyroid; carotids and jugulars not visibly pulsating. *Chest,* negative. *Heart:* Apex-beat in the fifth interspace (in the sitting position), three fingerbreadths to the left of the sternum; remains in the same location in the lying position, very circumscribed, not forceful or heaving, slow, regular. No diastolic shock, thrill, or bruit palpable. Heart borders (to percussion) apex-beat, fourth rib, midsternal line. Sounds, apex—slow, pure, regular, slightly distant. Very slight accentuation of the second tone over both the pulmonic and aortic areas; *very slight systolic murmur over the pulmonic area, disappears entirely on deep inspiration. Tit-tat phenomenon over the gladiolus.* Large vessels of the chest not widened on percussion, normal to auscultation; jugulum negative, no murmurs or other abnormalities over the large vessels of the neck. *Abdomen:* Viscera negative.

LABORATORY FINDINGS.—*Urine.*—(*a*) Single specimen, color straw, specific gravity 1.010, reaction acid. Faint trace albumin, few leukocytes. Dextrose, casts, and erythrocytes negative.

(*b*) Twenty-four-hour specimen, 1,600 c.c., color straw, specific gravity 1.010, reaction acid. Trace albumin, few leukocytes. Dextrose, casts, and erythrocytes.

Feces.—Three specimens (following blood-free diet), brown, formed. Mucus, pus, ova, and parasites negative. Occult blood positive.

Blood:

Erythrocytes	5,100,000
Leukocytes	7,000
Hemoglobin	103 per cent.
Stained smear	normal
Wassermann	negative

Blood-sugar:

(*a*) First specimen	0.064
(*b*) (Following 500 grams (17½ ounces) glucose in twenty-four hours, with injection of adrenalin 1/1000, m. x.)	0.076

SPECIAL EXAMINATIONS.—*Fluoroscopic.—Head, neck, lungs, heart, vessels, mediastinum,* and *stomach* negative.

Roentgenogram.—Head: Sella turcica and frontal sinus small. No other abnormal markings.

HISTORY: CASE XXII.—Mrs. D. M., housewife, aged twenty-seven, St. John's Hospital, General No. 1262, February 22, 1918. (*Bilobar Insufficiency.*)

Present.—Chief Complaints: (1) *Headaches,* sensation of pressure in the head, located at the vertex, brought on by nervousness. (2) *Aberrant attacks of unconsciousness, during which the patient at one time wandered away from home.* (3) Attacks of severe cutting *pain in the small of the back,* at times referred down along the course of the ureter. Occasional pain and frequency of urination. No history of the passage of stones or gravel, but the patient passed blood some time ago. (4) *General nervousness.* (5) *Marked loss of weight, 40 pounds within the past three months.* (6) Constant *pain over the precordia,* becoming sharp on exertion. (7) Occasional *edema of the legs.* (8) *Shortness of breath.* (9) *Rapid gain of weight after marriage. Five years ago* the patient weighed *117 pounds;* last November, *212.* Since that time her weight has fallen to 172. *Localized obesity about the hips and above the waistline.* (10) *Menstrual disturbance,* marked within the past two or three months, *intervals between the periods varying from one to two weeks, flow scanty and painful.* (11) *Puffiness of the hands,* especially in the morning. (12) *Dryness and harshness of the skin* over the entire body. (13) Some change in complexion to a *brownish discoloration* (about the face). No change in the hair. (14) *Constant tympanites.*

Duration.—Five years.

Course.—(*a*) *Onset:* Somewhat sudden. The patient, as far back as she can recall, has been subject to headaches, located at the vertex of the skull, but not especially severe. Eight months ago she was suddenly seized with a very severe headache, located at the vertex. The pain was sufficiently severe to cause the patient to walk around in an unconscious state. During this attack there were intervals of consciousness lasting a moment or two, again followed by unconsciousness. This attack came on at about eleven o'clock in the morning, and lasted until three o'clock of the next morning, during which time the patient was practically unconscious. The headache still continued, but was not so severe. The pain seemed to start in the back, extending up the spine to the vertex of the skull, described by the patient as very severe, throbbing in character, "as if the top of the skull were coming off."

(*b*) *Progress.*—Since this attack there has been continued pain in the vertex of the skull, not sufficiently severe to cause marked distress, except during the severe attacks, none of which have been as severe as the one above described. One week ago, while on the way to consult a physician, the patient was suddenly seized with one of these attacks, in which she lost consciousness, wandered to the depot, bought a ticket, and came to St. Louis. On her arrival in St. Louis, she telephoned to her home town in Missouri, telling the operator she would come home. After doing this she did not remember having done so. At times the patient is able to tell when such attacks are coming on by an increase of nervousness. She states that the attacks are brought on by overwork, nervous shock, or strain. There is no relation of the headaches to the menstrual flow, but they are accompanied by some *disturbance in vision.* During the last attack the physician said that the sight of the left eye was temporarily gone; but the patient herself has never noticed any marked disturbance of vision. The headaches are not accompanied by gastric disturbances. Five years ago, following a curettement, the patient developed a pain in the back, for which she was in bed ten weeks. After this time, on walking about, she noticed sharp, severe attacks of this pain, for which she was forced to take hypodermic treatment for relief. The pain originates in the back, bilaterally, is worse on the right side, extending around the lower margin of the ribs and shooting down along the course of the ureter. It is not accompanied by urinary signs, such as hematuria or gravel. This condition continued, the pain coming on at irregular intervals. One year ago the patient suffered another severe attack, in which blood was passed in the urine. This hematuria continued for a short time. The pain was sufficiently severe to require hypodermatic relief. No hematuria since that time, but the patient has suffered an occasional attack of very severe pain of the same type as described. (She has not consented to hypodermics, on account of the gastric disturbances which follow these.) At no time has there been a history of the passage of gravel or stones. No history of distinct chill or fever during these attacks, but at times the entire body is covered with a cold moisture. Five years ago, at the time of the rapid gain of weight, she also noticed symptoms referable to the heart. On exertion or overwork there is palpitation of the heart, with some irregularity. At times she is unable to feel any action of the heart at all. There has also been dyspnea and pain over the precordia. This disturbance continued in like manner for four years; it was not very acute, but present following exertion. One year ago these attacks became more severe. The patient at times seems to be conscious of arhythmia, which is followed by coldness of the body, and swelling of the extremities, extending to the knees. Since that time she has been subject to attacks, coming on at irregular intervals. Some relation between the severe headaches and the cardiac trouble has been noted, but at times they are independent of each other. No history of hemoptysis. Five years ago the patient weighed 117 pounds. *Rapid gain in weight* then occurred, with tendency to *localization about* the *hips* and the chest, extending down to the waistline. In five years there was a gain of 90 pounds; but within the past eight months she has lost about 40 pounds. The patient has also noticed *puffiness of the hands,* dryness and harshness of the skin over the entire body, some change in complexion to a brownish color, and general tenderness of the whole body, bruising easily. At present the periods are very irregular, coming on from one to two weeks apart (for the past four months). This *complete change in the menstrual periods* four months ago came on with severe headache. The patient is of the opinion that there is some relation between the flow and the headache; yet they are at times absolutely independent of each other. The periods at present are very scanty and painful. The menses began at the age of fourteen, were rather irregular at first, later becoming regular, of the twenty-eight-day type, lasting from three to four days, with some pain. Following the curettement mentioned above, the periods again became irregular, the intervals at times being shortened, at times lengthened, some dysmenorrhea. The patient is subject to constipation at times, also to tympanites. No symptoms referable to other systems.

Past.—Measles, mumps, chicken-pox, whooping-cough, pneumonia, typhoid, slight malaria, pleurisy, rheumatism, tonsillitis.

Personal.—Coffee in large quantities, no alcohol. Appetite fair, bowels constipated, restlessness at night, no disturbance of urination. Patient married, has no children, had one miscarriage (three months). Curettement as noted above.

Family.—Father and mother living, well. Five brothers living, well. History of cancer, on father's side. No history of hereditary diseases or dyscrasias.

EXAMINATION.—*General.*—Obese individual, obesity not especially localized. Height, 5 feet 6 inches; weight, 172 pounds. No marked changes in skull development, except that the head is rather round and full. The nose has a concavity along its bridge, with tendency to project upward. The neck is rather full, no perceptible thyroid enlargement. *Considerable girdle obesity;* mammæ very much enlarged; fat pads hanging from the lower portion of the chest posteriorly. No abnormal distribution of hair. Skin very dry and harsh, with tendency to grating sensation on palpation, rather thick, inelastic, and extremely tender. *Hands small, slight puffiness about the backs of the hands.* Feet of moderate size, deformity of left great toe, due to old injury. No abrupt demarcation of obesity at the middle of the forearm or of the thigh, none at the wrist. Pigmentation—no distinct chloasma, but very slight yellowish tinge to the skin of the forehead and face, eyelids slightly darker than other portions of the face. Hair of the scalp, eyebrows, and eyelids, not abnormal. *Pulse, slow,* regular, equal, symmetrical, low volume and tension, slightly increased in rate, with tendency to stenotic type. No abnormal gait, station, or position. No marked abnormal development of the long bones; patient very well proportioned, with the exception of the obesity. No abnormal pigmentation about the body, but slight pressure produces erythematous region. Temperament psychoneurotic, not especially well controlled. Pulse, 84-102; temperature, 97.8°-99.2° F. (36.5°-37.3° C.); respiration, 20-28.

Regional.—*Head:* Marked tenderness at the vertex and over the supra-orbital nerves. *Ears:* Air conduction (to tuning fork, C-128) decreased to two inches in each ear; bone conduction decreased in both the right and left ears, but not absent entirely; Rinne's test negative bilaterally. *Nose:* Tendency to high saddle shape. *Mouth:* Toothline perfect, no overcrowding of the lower teeth; angle of the jaw wide, producing *marked separation of the upper incisors.* No decay of the dentine. Lower jaw rather prominent, but no prognathism or blunting of the tip. *Neck:* Thyroid not enlarged or abnormal in vascularity. *Heart:* Apex-beat (in the lying position) four fingerbreadths to the left of the sternum; no diastolic shock, thrill, rub, or bruit palpable. Heart borders—apex-beat, fourth interspace, right border of sternum. Sounds, apex—slow, pure, regular, distant. *Very slight systolic murmur heard over the base, disappears entirely on deep inspiration,* heard most distinctly over the midline of the sternum; slight accentuation of the second tone. Murmurs not transmitted up along the vessels. *No distinct tit-tat phenomenon.* Blood-pressure—systolic 126, diastolic 90. *Abdomen,* and visceral organs negative. Physical examination of *nervous system* negative.

LABORATORY FINDINGS.—*Urine.*—Twenty-four-hour specimen, 1,170 c.c., color straw, specific gravity 1.010, reaction acid. Trace albumin, few leukocytes. Dextrose, erythrocytes, and leukocytes negative.

Feces.—(Three specimens). Following blood-free diet—mucus, pus, ova, and parasites negative, occult blood positive.

Blood:			
Erythrocytes	5,600,000		
Leukocytes	11,000		
Hemoglobin	100 per cent. (Sahli)		
Stained smear	normal		
Wassermann	negative		
Differential count:			
Polymorphonuclears	58	per	cent.
Small lymphocytes	18	“	“
Large lymphocytes	17	“	“
Myelocytes	3	“	“
Transitionals	3	“	“
Mononuclears	0	“	“
Eosinophils	1	“	“
Basophils	0	“	“
Chemical Blood:			
Blood-sugar	0.094		
(Following 500 grams ($17\frac{1}{2}$ ounces) dextrose in twenty-four hours, by mouth, an injection of adrenalin 1/1000)	0.076		

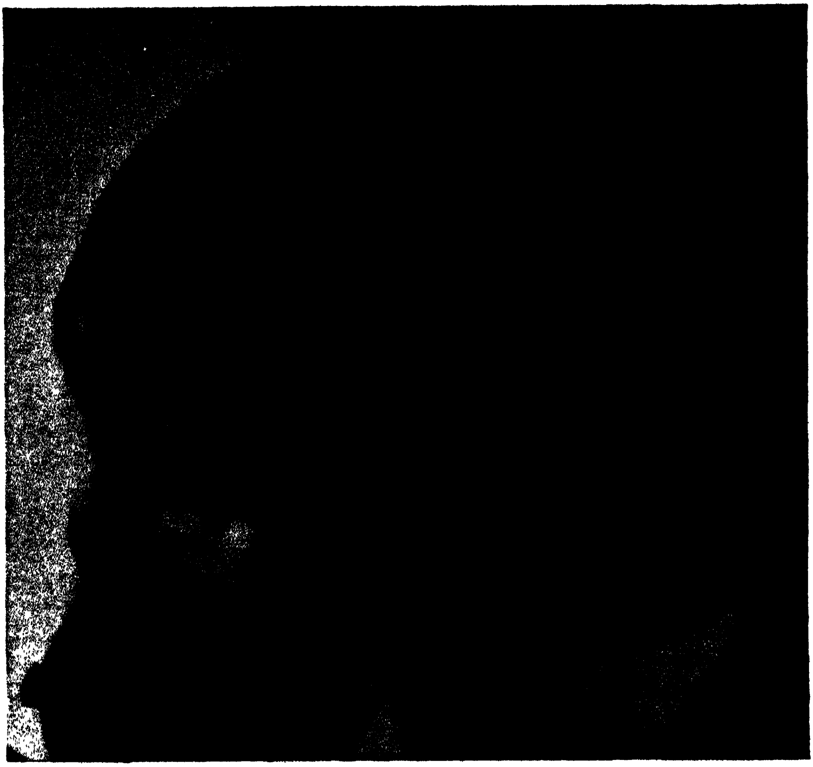
SPECIAL EXAMINATIONS.—*Roentgenogram of Skull* (Transverse View).—Frontal sinus and antrum free from shadows. *Sella turcica not enlarged.* Mastoid cells and base of skull negative.

Roentgenogram of Skull (Anterior-posterior View).—Negative.

Roentgenogram of Right Kidney and Ureter.—Negative for renal or ureteral calculi. No enlargement of the kidney.

Ocular Examination (Dr. E. P. North).—Lid fissure normal, some conjunctivitis present. Pupils equal, react to both light and accommodation, consensual reaction normal. Extra ocular muscles seem to react normally, but there is diplopia on looking to extremes. Field for form in the right eye normal; in the left, however, eye is contracted. Ophthalmoscope shows right eye, media clear, optic disc clear in outline, right fundus normal; left eye, media clear, optic disc both below and above disc. Below disc, shows petechial hemorrhages, veins about disc engorged and tortuous. Vision right eye, 20/24; vision left eye, 20/49.

Rhinological Examination (Dr. C. F. Pfingsten).—Impacted middle turbinate, right side. Well marked evidence of frontal sinusitis, also some symptoms referable to the sphenoid and postethmoid cells; anterior group of ethmoid sinuses apparently not involved. Antrum shows slight involvement. Ears, throat, and larynx normal.

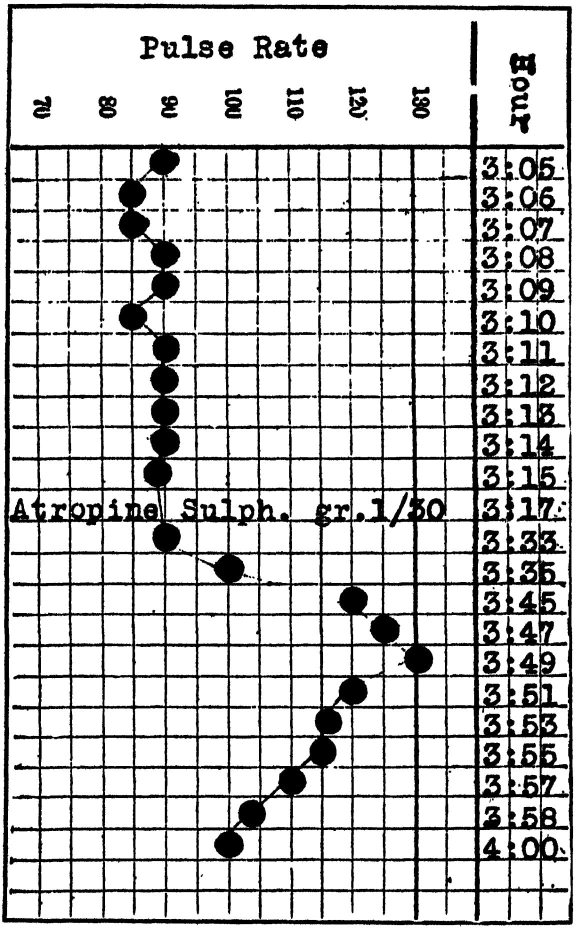


CASE XXII. FIG. 1.—NOTE SMALL SELLA TURCICA.

Atropin Test.—Negative.

Diagnosis.—These 6 cases will be considered as a group. They all belong to the division of hypopituitarisms. Three of the male cases (XVII, XVIII, and XX) are unilobar cases, involving the anterior lobe alone. One male case (XIX) and the 2 female cases (XXI and XXII) belong to the bilobar subdivision. The 2 female cases have besides the hypopituitarism, a mild (Case XXI) and a decided (Case XXII) secondary hypothyroidism. It is unnecessary at this point to go into detailed diagnostic analysis with regard to the individual cases, so that only the following summary, with the basis of a diagnosis of pituitarism, will be given.

In Case XVII the family history and personal observation of the individual members of the family portray a very decided lineal and familial group of acromegalics. The patient's father, one brother, and two sisters are typical acromegalic individuals, having very decided markings in the retardation of the general skeletal growth, and in the changes in the head, hands, feet, etc. Physical examination of the patient himself demonstrates a very classically proportioned type of acromegalic build—stunted stature, typical pituitary head, classical nose and chin, and very classical hands and feet. The slow pulse, subnormal temperature, and



CASE XXII. FIG. 2.—GRAPHIC CHART OF PULSE-RATE BEFORE AND AFTER ADMINISTRATION OF ATROPINE SULPHATE, 1/30 GRAIN.

high sugar tolerance, indicate in this case a hyposecretion of this lobe at the time of observation. There is absence of an enlarged sella turcica or any intracranial pressure symptom upon the optic thalamus or motor ocular nerve. The disturbances of the senses of taste and smell were also absent in this case. The history and the physical and special examinations show no other demonstrable causes for the epileptiform attacks.

The history of Case XVIII demonstrates that he is the brother of the patient with pituitary epilepsy (Case XXI) reported in this section. The physical examination in this case is very positive for pituitary dyscrasia. The arrested skeletal growth, the shape of the hands and feet, the type of nose, the projection of the inferior maxilla, and the separation of the teeth, are classical for anterior lobe involvement. The slow pulse, the subnormal temperature, the high sugar tolerance, and the temperature reaction to anterior lobe extract, indicate that there is a decreased secretion of this lobe. There is no other evidence of intracranial pressure symptoms, as shown by the normal sella turcica and the absence of pressure upon the neighborhood nerves or the uncinate gyrus. This patient did have a very decided aural aura, such as hearing voices, frequently his mother's voice, just previous to the onset of the epileptic attacks. There were no perversions of smell or other special senses during the aura.

In Case XIX the history is that of a recent petit mal attack, beginning six months previous to observation. The aura in this case consists of nausea and a peculiar "catching in the stomach," which is followed by loss of consciousness. Immediately following its disappearance, or the recovery of consciousness, the patient has, *after each attack, a very disagreeable taste,* which lasts sometimes for twenty or thirty minutes. There is also a history in this case of a gain in weight during the last year, which might suggest involvement of the posterior lobe. In addition to these attacks of epilepsy, the patient complains of sudden complete loss of libido, which has been persistent throughout the six-month course. The physical examination shows the type of individual one would suspect of having had some abnormality of the anterior lobe of the pituitary some time previous to the onset of the disease. The stature is short, and the hands and feet, small, as compared with the weight. The head is a classical pituitary head—rather straight, sharp, pointed nose; separation of the upper teeth; and well formed, projecting lower jaw. The abnormal distribution of hair over the chest, abdomen, and extremities is marked. Slight pigmentation is present about the forehead, around the angles of the jaw, and on the lateral aspects of the neck. The constant subnormal temperature and the slow pulse, taken with the loss of libido, speak for insufficiency of the anterior lobe. The increase in weight and the girdle obesity show that there was probably also an involvement of the posterior lobe. There was no evidence of enlargement of the sella turcica or pressure upon the neighborhood chiasm or the third, fourth, or sixth nerve. The *marked gustatory symptoms,* referred to as a "catch in the stomach" during the aural stage, and the constant disagreeable taste during recovery from the convulsions, indicate a possibility of pressure upon the uncinate gyrus.

In Case XX the history shows the possible relationship to early trauma, the patient having sustained an injury during childhood and a burn of the head during his boyhood days, just previous to the onset of the first attack of epilepsy. There is no definite history of arrest of growth at any one stage during his development, no change in weight or addition of adiposity. The physical examination demonstrates the classical makeup of the acromegalic individual, showing the classical head, nose, and chin, and the separation of the front teeth, with the short, broad hands and pudgy fingers, and the wide foot with short, flat toes. Contrary to a gain in weight, there has been a gradual loss of 15 pounds during the course of four years previous to the time of observation. The slow pulse, the subnormal temperature, the marked general depression, and the high sugar tolerance all indicate an insufficiency of the anterior lobe. There was no evidence of an enlarged sella turcica or intracranial pressure upon any of the neighborhood structures, except that of the uncinate lobe, demonstrated by the *marked gustatory disturbances*, in the form of *a peculiar odor and taste occurring* during the aura

Case XXI gives a typical history of amenorrhea and scanty periods, more or less associated with a rapid gain in weight of thirty pounds in one year. The physical examination demonstrates a typical pituitary type of individual, with characteristic head, nose, chin, and separation of the upper incisors. The hands and feet are also very suggestive. The girdle obesity is classical. Besides these symptoms, she also has evidence of hypothyroidism, which is regarded as secondary to her hypopituitarism. This is demonstrated by the enlarged thyroid and the typical thyroid heart having a systolic murmur over the apex and pulmonic areas, which disappears entirely on deep inspiration, and a "tittat" phenomenon over the gladiolus. The slow pulse, subnormal temperature, and increased sugar tolerance, combined with the obesity, help to prove that the involvement of both lobes of the pituitary consists of hypofunction. There is no evidence of intracranial pressure symptoms or of an enlarged sella turcica. The patient has an aura consisting of nausea; but this is probably more the effect of general intracranial disturbances than of localized pressure upon the hippocampal gyrus.

Case XXII is very similar to Case XXI in being a bilobar insufficiency associated with a secondary hypothyroidism; but the history shows that the onset of this condition occurred later in life than that of Case XXI. The patient has the typical makeup of pituitarism, consisting of bony markings in the head, nose, and chin, the separation of the upper incisors, the characteristic type of hands and feet, and the abnormal distribution of hair about the face, body, and abdomen. Her obesity is not that limited to the girdle region. There is also some supraclavicular fat padding, and the dorsa of the hands are padded at times. This adiposity indicates insufficiency of the posterior lobe, plus insufficiency of the thyroid gland. Other indications that the thyroid is involved are the slight enlargement of the gland itself and the typical thyroid heart, detailed description of which is given in the case report. The important signs in this heart are the slow, regular pulse; the lack of change in size, form, or shape of the heart; the systolic murmur over the apex and pulmonic areas, transmitted upward toward the clavicle, associated with the "tit-tat" phenomenon over the gladiolus, which mimics a very short, soft pericardial friction rub. *The systolic murmur disappears entirely on deep inspiration,* which differentiates it from a true endocardial murmur. There is no diagnostic evidence in this case of an enlargement of the pituitary gland, as demonstrated by the normal size of the sella turcica and the absence of intracranial pressure symptoms. Symptoms referable to intracranial disturbances, and possibly, in this case, to intracranial pressure (although there is no evidence of an enlarged pituitary gland), consist of epileptic aura, headache, and other nervous symptoms distinctly referable to the pituitary gland.

It will be noted in this group of cases that Cases XVII, XVIII, and XIX had absolutely no complaints of headaches or other intracranial signs. These are all male cases, in 2 of which the anterior lobe alone showed evidence of involvement, and in one of which (Case XIX) there were, besides the anterior lobe, minor evidences of posterior lobe affection. In Cases XX, XXI, and XXII terrific headache was one of the most disturbing complaints. In these 3 cases this headache was associated with disturbances of vision and more or less gastro-intestinal disturbance, making up a migraine complex. The location of the headache was variable. In Cases XX and XXII it varied considerably in location, and in Case XXI it was constantly localized as a hemicrania. In Cases XXI and XXII, both bilobar cases in which there is a secondary hypothyroidism, the headache occurred as one of the pronounced aural symptoms initiatory to the epileptic convulsions, the aberrant loss of consciousness lasting for twenty-four hours in Case XXII. It has been previously noted that this headache is more constantly related to insufficiency of the posterior lobe than to that of a pure anterior lobe involvement. Analysis of the writers' cases also tends to prove that anterior lobe insufficiency, without posterior lobar affection, in the aneoplastic type of pituitary disease, is very rarely associated with headache. With regard to the localizing symptoms occurring during the epileptic aura, 2 of these cases (XIX and XX) have symptoms referable to the senses of taste and smell, which are supposed to be of great diagnostic importance as indicative of pituitary epilepsy. Case XIX had constant gustatory disturbances—a very peculiar, indescribable taste following the attacks of petit and grand mal. Case XX had a definite aura, consisting of both gustatory and ophthalmic sensations, just preceding the epileptic attack. In case XVIII there was a constant aural aura, during which the patient had tinnitus or heard a voice repeatedly, as the initial symptom of his epileptiform attack. Case XXI frequently had gastric disturbances previous to attacks. Cases XVII and XXII had only a general aura, consisting of vertigo, extreme nervousness, and irritability, which in Case XXII was associated with an intractable headache. While it is very important to attempt to elicit special symptoms related to the gustatory sense, the fact that they are absent in 4 of these 6 cases does not have definite bearing upon the differential diagnosis. The preponderance of many other hormonic signs, and the present and family dystrophies of these cases, should be sufficient to connect their epileptic attacks with the pituitary gland. If the diagnosis in these cases can be accepted, it will be upon the basis that pituitary epilepsy does occur without gustatory signs. Another factor in these cases is that the very short time of observation might be an explanation for the absence of this sign in some of them. The absence of these gustatory aural symptoms has been reported in controlled cases in the literature. The other nervous disturbances, less important as diagnostic signs, but commonly associated with pituitary epilepsy, as well as other hypopituitarisms, are well worth recognition. In Cases XVII and XX somnolence was present. In Case XVII, this, with the loss of concentration, was frequently a precursor of the attack. In Case XX it was associated with depression, inertia, and indifference of mentality. In the interval between the attacks, with the exception of Case XX, the members of this group showed a highly organized nervous system, with irritability, emotionalism, and psychoses as elements of the nervous constituency. In nearly all of these cases these extreme nervous disturbances, associated with headache, were more or less constantly found present just previous to the epileptic attack. In the 2 female cases of the group, these nervous disturbances were definitely related to the premenstrual week.

The specific hormonic signs indicating lobar involvement of the pituitary gland in the above group of cases refer to those changes in the gonads and the skeletal growth as anterior lobe hormonic signs, and obesity as evidence of posterior lobar insufficiency. In Cases XVII, XVIII, XIX, and XXI there were very characteristic skeletal changes, indicating previous hypoactivity of the anterior lobe, shown by the development of the bones of the head, hands, and feet, and the retarded growth of the long bones. In Cases XVII and XVIII there were no evidences of insufficiency of the gonads, as shown by the size or development of these organs in the male. In Case XIX there was a definite history of sudden loss of libido occurring with the onset of epilepsy. In Case XX there was a history of impotence, with lack of development of the secondary sexual characters. In Cases XXI and XXII there was very decided reduction in the menses, resulting in the marked change in amount, duration, and regularity of the menstrual flow. The hormonic signs indicative of posterior lobe insufficiency were present in only those 3 cases in which there was bilobar involvement. In Cases XVII, XVIII, and XX there was complete absence of obesity, and in Case XX there was even loss of weight during the last four years (15 pounds). In Case XIX (male) the history shows an obesity ten years previous to the onset of the epilepsy and recent loss of libido. This would indicate the possibility of a hyposecretion of the posterior lobe, without an involvement of the anterior lobe, occurring at that time, and later an insufficiency of the anterior lobe, with the onset of the attacks of petit mal, indicated by the complete and sudden loss of libido which occurred coincident with these attacks of epilepsy. In Case XXI there was a marked sudden development of adiposity, amounting to 30 pounds within one year following pregnancy. This occurred two years previous to the epilepsy, also indicating that the anterior lobe in this case probably became involved much later than the posterior lobe. The interpretation of Case XXII is rather difficult, and might indicate a change of activity of secretion of the posterior lobe. The history narrates that the patient gained weight rapidly following her marriage at the age of twenty-four—from 117 to 212 pounds. This gain in weight consisted almost entirely of a classical girdle obesity. After the first year of progressive adiposity, the patient began to lose gradually, and during the following four years gradually decreased in weight to 172 pounds. There was no polyuria, polyphagia, or other hormonic sign associated with this loss of weight, indicating hyperactivity of the posterior lobe. Her menstrual disturbances occurred a number of years following the marked change in adiposity. This patient has a secondary hypothyroidism, which might also be responsible to a certain extent for the change in weight.

A glance at the differences in the male and female involvements in these cases shows that of the 4 male cases, 3 showed a pure anterior lobe involvement, the fourth having evidence of a mild secondary posterior lobe insufficiency. Both of the female cases had very classical bilobar involvements, as evidenced by the marked disturbances of the menses, indicating anterior lobe insufficiency, associated with the classical girdle obesity, changes in metabolism, such as increased sugar tolerance, slow pulse, subnormal temperature, etc., implicating the posterior lobe. Among the other hormonic symptoms present in this group are disturbances of the gastro-intestinal tract, muscular pains, and dyspnea. By referring to the case records, it will be seen that these are not limited entirely to the bilobar cases. Three patients attributed their epileptic attacks to constipation. Case XVII gave a history of chronic constipation, associated with a mucous colitis, and has been treated a considerable length of time by a proctologist for this condition, in the hope of preventing the epileptiform attacks. Case XXI could well be grouped with the painful abdominal pituitary cases, on account of the severe pain in the right inguinal region. This was associated rather definitely with the periods, and was frequently absent entirely for one or two weeks following the menses. In case XXI, also, there were severe attacks of indigestion, which were at times accompanied by right hypochondriac pains, abdominal distention, and other signs very similar to mild attacks of cholecystitis. In fact, one could not be absolutely sure that these abdominal attacks in the right hypochondrium were not due to such a disease, as the primary or associated cause. The pain in the back is a very consistent complaint in the female bilobar varieties. It has been previously referred to as one of the common constitutional symptoms associated with bilobar hypopituitarism. It was negative in the 4 male cases in this group—another sign for anterior lobe insufficiency. Dyspnea was another complaint which occurred intermittently in the female bilobar cases. It was absent in the 4 male cases. It is very rare to find extreme constitutional symptoms with the anterior lobe dyscrasias, either in hypo- or hypersecretions. On the contrary, the constitutional symptoms, such as gastrointestinal disturbances, constipation, dyspnea, lumbago, indigestion, nausea, vomiting, substernal pressure, syncopal attacks, etc., are the chief complaints of the bilobar insufficiencies, particularly when they occur late in life.

Complications and Sequelæ.—There are no definite complications in this group of cases. The marked nervous disturbances of petit or grand mal attacks of epilepsy, or aberrant attacks of unconsciousness, during which the patient (Case XXII), for twenty-four hours, wandered away from her home to another city, might be considered sequelæ. The cause of the epilepsy, which is supposed to be due to pressure upon the uncinate gyrus, might also be classified as a complication or sequela in these cases. The fact that none of these cases had objective enlargement of the pituitary gland, and that only 2 had distinct gustatory symptoms, supposedly hippocampal pressure effects, allows the definite evidence of lateral pressure from the pituitary upon this structure of the brain to be questioned. Whether any of these 6 cases will finally develop pituitary tumor, producing other complications and sequelæ, cannot be determined. Prolonged observation of the course, with frequent roentgenographic and neurological examinations to determine the local change in the gland, as well as careful observance of the hormonic signs relative to the lobar involvement and the activity of the individual lobes affected, will aid in determining these possible sequelæ.

Associated Diseases.—Associated diseases in this group of cases occurred in Cases XXI and XXII, of the female sex, consisting of hypothyroidism. These are both postadolescent bilobar hypopituitarisms, beginning, however, in the early adolescent life. It is rare that this variety of case at this age in life has marked decrease in the thyroid secretion. There was evidence in both these cases, as shown by the cutaneous changes, the supraclavicular fat padding, and in one case (XXI), the effect of thyroid secretion, that the thyroid was secondarily involved. In Case XX there were some signs of a possible focal lesion in the right Rolandic area, as shown by an intermittent loss of motor power of the left arm. This sign throws the diagnosis of this entire case into question, *i. e.*, it might be a secondary insufficiency of the pituitary gland, due to brain tumor. Case XXII gave a history of hematuria, associated with renal colic. At the time of observation there were no evidences in the laboratory examination or the roentgenological picture of the genito-urinary tract, of lesion in this system. It is probable, if there was a kidney or ureteral lesion in this case, that it was one entirely independent of ductless gland disease. Case XXI, however, gave a history which might be interpreted as a possible gall-bladder disease. This opens the question of the relation of ductless gland diseases to those having calculus deposits. The etiology for calculi diseases has been for many years placed upon the infectious basis. It has been definitely proven that infections of the gall-bladder, or the pelvis of the kidney, are undoubtedly the exciting cause for later deposition of calculi in these organs. On the other hand, it is well known that the hyposecretory diseases of the ductless glands have such a decided effect in reducing the metabolism as to induce the precipitation of deposits of the solids from the biliary and renal secretions. The frequency of the presence of gall-stones in the obese, and the occurrence of these calculi following pregnancy, have been frequently referred to by many authorities. With the knowledge that adiposity in most cases is due to an insufficiency of the posterior pituitary, the thyroid, or the gonads, it would seem that there might be a possible bearing of this ductless gland insufficiency upon the calculi-forming diseases. The general metabolism is possibly a predisposing factor, particularly for those cases in which calculi form in different organs. As all ductless glands undoubtedly regulate metabolism, their bearing upon these diseases may develop into some importance. The writers have records of many other positive cases of hypopituitarism, in which there was very positive gall-bladder disease. The relationship of hypothyroid cases to positive gall-bladder disease, in their experience, has been of a higher percentage. A number of cases of myxedema, associated with gall-bladder disease, will be reported later, and at that time more consideration will be given to this subject.

Clinical Varieties.—The anatomico-physiological grouping based upon the writers' classification in Chapter I will classify these 6 cases as follows: XVII, XVIII, and XX as simple anterior lobe insufficiency, without involvement of the posterior lobe; XIX, XXI, and XXII as bilobar involvement of hypopituitarism, of the postadolescent type. It will be noted that 3 of the 4 male cases are pure anterior lobe insufficiencies; and that 2 of the 3 bilobar cases are of females. This bears out the contention that the male sex is more liable to the pure anterior lobe involvement, whereas the female is more liable to an insufficiency of both lobes of the hypophysis. There is no definite evidence in any of these cases of a very marked preadolescent inactivity of the pituitary, with the exception that Cases XVII and XIX both have marked stunting of stature, which might indicate at least a partial insufficiency of the anterior lobe previous to maturity. Neither of these cases, however, has the objective evidence in the gonads to support the diagnosis of a marked insufficiency of this lobe in early life. There is every proof that all of these 6 cases had decreased secretion of the pituitary at the time of observation. While 3 cases (XVII, XVIII, and XX) give some evidence of the acromegalic type, careful interpretation of these cases at the time they were observed proves that there was inactivity of the pituitary instead of hyperactivity. This is shown by the hormonic signs in the skeleton, the deposition of fat, the slow pulse, the subnormal temperature, and the sugar tolerance. None of these cases belong to the neoplastic type.

Treatment.—Sufficient has been written regarding treatment in the previous sections to make it unnecessary to go into the detailed treatment of this group of cases. The 2 cases (XXI and XXII) *associated with secondary hypothyroidism,* according to the writers' method of treatment, should first be treated independently for this **deficiency of secretion of the thyroid.** After the secretion of this gland is properly balanced, or if, after a reasonable length of time (two or three months) this treatment has been given without satisfactory reaction, then treatment *directed toward the pituitary gland should be added.* As both of these cases are bilobar types, and as the insufficiency of the posterior lobe is producing more disturbance than that of the anterior lobe, it would be well to attempt first to **compensate the posterior lobe insufficiency** by exhibiting this preparation, as directed in the detailed technic in the previous sections. If this is possible and is accomplished, then **anterior lobe extract,** given intramuscularly, and **glandular substance of anterior lobe,** given by mouth, should be added later. The general indications for doses in combinations of these different glandular products must be judged in these 2 cases, as well as in the others, according to the specific indications and reactions obtained in the individual case. In the 3 cases (XVII, XVIII, and XX) in which the anterior lobe is insufficient, without evidence of involvement of the posterior lobe, or without other ductless glands being secondarily affected, the indications would be to give anterior lobe treatment, without treatment directed toward the posterior lobe or the thyroid, according to the indications described in previous chapters.

The writers have under observation Cases XVIII and XXII, the former a pure anterior lobe insufficiency and the latter a bilobar insufficiency. These 2 patients are brother and sister. They have been under treatment for two months. Case XVIII (*anterior lobe insufficiency*) is receiving minims xvi (1 c.c.) of **anterior lobe extract** intramuscularly once a week, with **anterior lobe pituitary,** grains ii ss (0.16 gram) three times a day, after meals. There has been no perceptible effect from this treatment observed in this case. Since leaving the hospital the patient has had one attack of epilepsy. He has never had any decided hormonic signs or symptoms that were very disturbing, so it is difficult to judge whether or not the treatment has had any effect. In Case XXI (*bilobar insufficiency, with secondary hypothyroidism*), the patient has been given the following treatment: **thyroid gland,** grain ½ to ¾ (0.03-0.048 gram), after meals; minims viii (0.5 c.c.) **pituitrin** (extract of posterior lobe) intramuscularly once a week. There has been quite a decided effect in relieving the general hormonic signs and symptoms of this patient. Her nervous stability is much improved, she has been absolutely free from headaches, and there has been freedom from dyspnea, gastro-intestinal symptoms, and lumbago during the past two months. She has had one period since leaving the hospital, which has not differed to any extent from those previous to taking the treatment. We would not expect, however, any effect from the treatment of thyroid and posterior lobe extract upon the periods. After this treatment has been continued for a sufficient length of time to demonstrate its effect and efficacy, anterior lobe extract and anterior lobe substance will be given, to test any additional effect upon the periods and associated symptoms. The length of observation of these cases is entirely insufficient to judge what the ultimate effects of treatment will accomplish. The other cases, except for the purpose of diagnosis, have not been under the observation of the writers. The associated diseases, such as constipation, mucous colitis, and possibly cholecystitis, etc., require individual treatment for the existing lesion. As previously stated, however, it is rare that ordinary treatment directed toward such conditions is very effective, unless the ductless gland dyscrasia can be modified by the specific treatment.

Prognosis.—The prognosis of pituitary epilepsy is in the same uncertain state as that of other pituitary diseases. The general prophecy with regard to these diseases is based upon the etiology and the activity of the pituitary disease. The aneoplastic types are very much more favorable with regard to the duration of life than the neoplastic. The hyposecretions offer more chance of relief by treatment than do the hypersecretions. Unilobar involvement of the pituitary is undoubtedly much more favorable than the bilobar involvement. The pure anterior lobe inactivity runs a much less disturbing course than the pure posterior lobar involvement. It has been noted in epileptic diseases associated with hyposecretions of the hypophysis that pure anterior lobe insufficiencies are the type in which the attacks occur only occasionally and at long intervals. The pure anterior lobe inactivity, not associated with neoplasm, is probably one of the most favorable types of epilepsy. The hypersecretory diseases of the pituitary associated with epilepsy, even though there is no definite enlargement of the pituitary gland or presence of intracranial pressure symptoms, should be given early surgical consideration. Hyposecretory types of pituitary epilepsy may be treated medically under careful observation for at least a considerable length of time, without the loss of the opportunity for good results to the patient who may require surgery. The prognosis as to the function of the pituitary gland is one that cannot be given with encouragement. If the function of either one, or both lobes of this gland, is decidedly decreased, it is not likely ever to be sufficiently restored to prevent a return of distressing local and constitutional disturbances. If this loss of function is purely a diminutive one which can be properly balanced by the substitution of the secretory product of this gland, these distressing hormonic symptoms may be controlled almost indefinitely.

Pathology.—The functional pituitary pathology as a cause for the epilepsy in these hyposecretions is one which is very debatable. The easiest explanation of the reason for the epileptic attacks in these cases would be, of course, that of direct pressure upon the uncinate gyrus, produced by an enlargement of the pituitary gland, in its lateral dimensions. In the cases herewith reported there is no objective evidence that there was any enlargement of the gland. There are only 2 cases which have definite gustatory disturbance, supposedly a localizing symptom due to pressure upon the hippocampal gyrus. There are other theories which attempt to explain the cause for the epileptic seizures due to hypophyseal disease, by the effect of the lack of stimulation of secretion from the pituitary gland upon previously injured areas of the brain. Cushing summarizes the data in regard to the possible relation of hypophyseal conditions to epilepsy as follows:

"(1) Horsley, it will be recalled, in his first experimental hypophysectomies in the canine, observed no postoperative changes whatsoever in the condition of the animals. They were, however, used subsequently as subjects of cortical stimulation, and he noted that the motor cortex was unusually excitable.

"(2) As already stated, we have observed a tendency to epileptiform convulsions in a number of our animals kept for long periods after partial hypophysectomy—animals that ultimately exhibited symptoms which we attribute to glandular insufficiency.

"(3) The study of a series of cases of hypophyseal disease in man has shown that epilepsy—a symptom unobserved in states of hyperpituitarism—is a frequent accompaniment of clinical conditions in which an insufficiency of the gland is manifest. Moreover, that the brain, under these circumstances, is possibly over-excitable, is suggested by the number of individuals in whom gustatory attacks have occurred under the influence presumably of a direct local irritation of the adjacent uncinate cortex by the enlarged gland.

"(4) As is well known, epilepsy is a frequent sequel of cranial injuries. In certain types of injury, as the common bursting fractures of the base, the pituitary body is prone to be damaged.

"(5) If, as we believe to be the case, the posterior lobe secretion normally enters the cerebrospinal fluid and this comes to be in solution in a fluid which subsequently bathes the cortex, it is possible that its diminution from hypophyseal disease or injury may unfavorably affect the activity of the cortical cells. On this basis it is conceivable that a local scar which involves, or a tumor which presses upon, a given area of the cortex, may prevent the access to the cells of a substance which is essential to their functional stability.

"(6) Many individuals, supposed to be suffering from so-called genuine or essential epilepsy, present manifestations of a nutritional disorder—a tendency to adiposity and a high sugar tolerance, coupled with a lower temperature and pulse-rate—closely akin to the constitutional state which characterizes hypophyseal deficiency. In some of these individuals, the administration of hypophyseal extract has served to moderate the seizures from which they previously suffered.

"It is of interest that Wenzel (1810) (cited by Biedl) looked upon the collection of colloid in the hypophysis as the cause of epilepsy."

As none of these cases were controlled either by operation or by autopsy, the morbid or macroscopic anatomy cannot be given. Clinical evidence demonstrated that in 2 cases there was secondary involvement of the thyroid, consisting of a decreased secretion of this gland. There were consequent symptoms in these cases of hypothyroidism, in the skin, the localized deposition of fat about the clavicles, arms, hands, etc. There was slight pigmentation in the 2 cases, about the forehead and face, which the writers have attributed to disturbance of the anterior lobe secretion, and not to the suprarenal. There was no evidence of any other endocrinous gland dyscrasia. In Case XX there was some motor disturbance of the left arm, without other focalizing evidence of cerebral lesion. The blood showed no special changes, except for a lymphocytosis in the majority of the cases. There was decreased sugar tolerance in all of the cases, except Case XX, which also gave a history of loss of weight instead of a recent gain. The organs of special sense were not affected. Other secretions of the body in any case, except the amount of mucus of the large intestine in Case XVII, producing a mucous colitis, were undisturbed.

SECTION 10

PITUITARY SOMNOLENCE OR HIBERNATION

(Bilobar Insufficiency, Postadolescent, Aneoplastic Type)

Etiology.—The etiology in this case is unknown. There is no family history of other ductless gland dyscrasias. Traumatic history is also entirely absent, with the exception of fracture of the leg, which probably had no relation to either the pituitary or the thyroid insufficiency. The past history was free from acquired diseases, with the exception of a number of children's diseases, small-pox, pneumonia, and pleurisy, all of which occurred years before the endocrinous dyscrasia. The patient's occupation, that of an electrical engineer, exposed him more or less constantly to electric rays of different kinds. Whether these rays had any influence upon inhibiting the secretion of the pituitary and the thyroid is a question. There are no definite similar cases reported in the literature. Inquiry of the writers has failed to reveal similar cases found in high tension dynamo factories producing electricity. It has been known for some time that the Roentgen-ray has this effect upon the secretions of the ductless glands, as best demonstrated by the production of spermatolysis and sterility in the male and female gonads, following prolonged exposures.

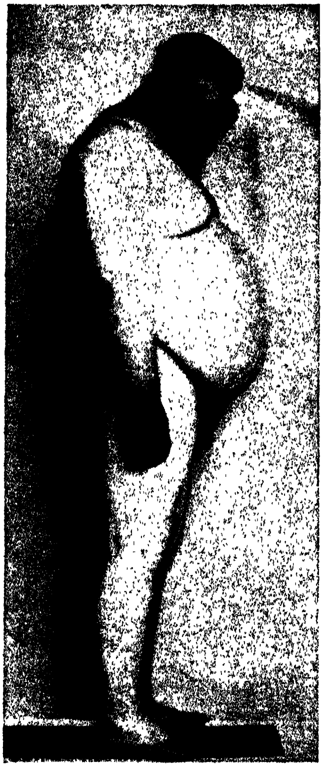
Symptomatology.—HISTORY: Case XXIII.—Mr. G. K., mechanical engineer, aged thirty-nine, St. John's Hospital, General No. 1637, referred by Dr. J. G. Turley, Flat River, Mo.

Present.—Chief Complaints: (1) *Extreme somnolence,* the patient going to sleep while walking. Head constantly falls over on the chest, in either the sitting or the upright position. (2) *Extreme insomnia during the night.* The patient awakes every few minutes during the night from dreams, and frequently falls from the bed shrieking and crying, disturbing those in the same house. (3) *Enormous obesity* (weight, 346 pounds). (4) *Marked thickness and harshness of the skin,* with marked fat padding about the neck, hands, and feet. (5) *Marked disturbance of speech,* inability to articulate on account of the thickness of the tongue. (6) *Dribbling of saliva* constantly from the mouth. (7) *Marked dyspnea.* (8) *Visual acuity so slight as to cause disability to read newspaper print.* (9) *Loss of libido and potentia.*

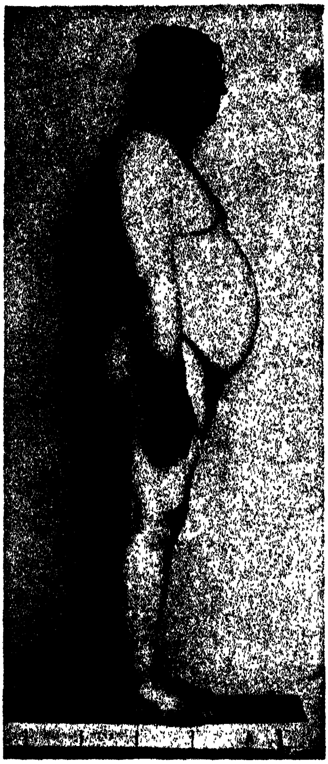
Duration.—Eight months.

Course.—(*a*) *Onset:* Gradual. The history is elicited with difficulty on account of the extreme somnolence of the patient, who has to be awakened every few minutes in order to finish a sentence. When asked a question, he starts to answer in a very intelligent manner, but after speaking two or three words, his speech changes into an inaudible mumbling tone and he goes to sleep before finishing the sentence. After he is awakened, it is necessary to repeat the question, on account of his lack of memory and concentration. He states that during these short intervals of sleep he has bad dreams, and on one occasion, after being awakened, motioned with the hand and talked of "forest fires." During this somnolent state the patient does not respond to ordinary stimuli, such as calling him by name, or noises in the room. To awaken him requires hard shaking. The history previous to adolescence could not be elicited. As far as can be determined, the obesity commenced at about the age of fourteen, at which time he weighed 120 pounds. At the age of twenty-three his weight was 170 pounds; at the age of twenty-seven, 220; at the age of thirty, 250. Eight months ago he weighed 291 pounds; three months ago, 310; and at the present time his weight is 346. There was a gradual but decided gain of weight up to three months ago, since when there has been a rapid addition of 36 pounds.

(*b*) *Progress.*—The extreme drowsiness and somnolence commenced eight months ago. While at work he would drop into a short sleep. After awaking from this, he would go about as before, but soon would be overtaken by another attack of uncontrollable drowsiness. A repetition of these attacks has occurred at short intervals, and the torpidity and somnolence have become more extreme, so that finally it was almost impossible for him to keep awake. He would sleep even while walking, during eating, and while attempting to engage in conversation. When lying down, he could not sleep continuously for any length of time. He would soon go to sleep, but would be awakened with what he describes as a "rush of blood to the head," which forced him to sit up, and frequently to roll and tumble out of the bed. This same sensation and persistent insomnia would occur on each occasion that he attempted to lie down and sleep. This became so persistent that for a number of months previous to coming under observation he had been sleeping in the sitting position; but this finally became impossible, on account of the frequent dreams, which caused him to awaken suddenly and fall from the chair. Until two weeks ago his voice was heavy and clear, and he had been noted, until then, as a good public speaker. After that time his voice became very inarticulate; he slurred and mumbled his words. This had progressed until at the present time it is almost impossible to understand him. In attempting to speak, he begins a sentence with one or two words distinctly, then runs a few words together in an inarticulate slurring way, and rarely finishes a sentence completely. The marked dribbling of saliva has been present only for the past week. No history of paralysis or evidence of involvement of the facial nerves. At the onset of the present trouble eight months ago, changes in the texture of the skin were noted. This became harsh, coarse, thick, and dry. This condition has increased very decidedly in the past two weeks, and at the present time the patient compares it to "leather." He perspires freely, especially over the face and the body as far down as the nipple line. Other portions of the body remain dry. In the standing position the patient's head is flexed on the chest. He is able to raise it to the erect position for only a few moments, when it drops forward again, hanging over the chest-wall. (This position is noticeable in the photograph. During the time the photograph was taken, the patient could not be kept awake.) Disturbances of vision have been present for the past six months. He first noticed blurring and that certain letters, particularly the *e*'s and the *a*'s, were indistinguishable. On holding the paper at a normal distance from the eyes, he states that the letters appear to be moving about the page. Loss of sexual desire has become complete for the past three months. Previous to this time, normal relations occurred and sexual intercourse had been carried out with regularity. Since that time loss of libido and impotence have been present.



CASE XXIII. FIG. 1A.—NOTE LARGE STATURE, ENORMOUS OBESITY, PARTICULARLY ABOUT HYPOGASTRIUM AND MONS, SOMNOLENT EXPRESSION, AND DROOPING HEAD.



CASE XXIII. FIG. 1B.—(AFTER TREATMENT.) NOTE DECIDED DECREASE IN OBESITY, PARTICULARLY ABOUT ABDOMEN AND MONS, DECREASED SOMNOLENCE, INCREASED ALERTNESS OF EXPRESSION, ERECT BEARING, ETC.

Past.—Measles, mumps, chicken-pox, diphtheria, in childhood.

Small-pox, pneumonia, pleurisy, in adult life. No operations, no injuries except fracture of the leg.

Personal.—Patient unmarried. Appetite fair, but not ravenous. Foods taken have not been excessive. His physician states that the patient's appetite is not enormous, in fact, not as large as those of other members of the family. The patient has always been very active, doing a considerable amount of hard physical labor. Bowels regular. No urinary disturbances. Smokes and chews moderately; no alcohol. No history of venereal disease. Constant exposure to electric ray in his occupation.

CASE XXIII. FIG. 2.—NOTE SPADE-LIKE HAND, BROAD PALM AND WRIST, SHORT AND STUBBY FINGERS, WITH TENDENCY TO BLUNTING, MAMMARY DEVELOPMENT, AND HIRSUTIES.

Family.—Mother living, well, weighs 165 pounds, is not disproportioned in stature. Father dead, weighed 145 pounds. Two brothers living, well proportioned, weighing 170 pounds. Two sisters living, weighing about 120 pounds. No history of marked adiposity in the family; no familial history of infantilism, gigantism, or other ductless gland dyscrasias.

EXAMINATION.—*General.*—*Enormously obese man,* 6 feet 2 inches in height, weighing 346 pounds. *Obesity universal,* involving particularly the lower half of the face, the neck, chest, abdomen, and extremities. *No marked fullness of the backs of the hands.* Fingers spadelike, stubby. Toes and feet stubby, arches very low (size of shoe, No. 11). No distinct edema. Slight dyspnea, particularly when the patient lies down, requiring an effort to breathe. *Skin very thick,* inelastic, fixed to the underlying tissue, difficult to separate or raise from the underlying tissue. Color good, no cyanosis. No abnormal gait or station. Position of the head is that of being constantly dropped forward over the chest, and the sitting position is modified by the obesity of the abdomen, which hangs forward over the edge of the chair, throwing the patient slightly forward. No pigmentation. Considerable abnormal distribution of hair across the chest and lower abdomen, only slight increase on the forearms; hair of axillæ and pubes normal. Pulse, slow, regular, rate 88, equal in rate, rhythm, and tension, slight tendency to stenotic type. Temperament phlegmatic. Marked somnolence. Head large, inverted triangular shape, with rounded chin. Skull itself not very large, but somewhat enlarged at the lower portion of the face and head. (Size of hat, No. 7¾.) Blood-pressure—systolic 158. Measurements: From vertex to symphysis, 35 inches (89 cm.); from symphysis to feet, 39 inches (99 cm.); humerus, 14 inches (36 cm.); forearm, 11 inches (28 cm.); femur, 18 inches (46 cm.); lower leg, 18 inches (46 cm.); circumference of skull, frontal region, 22½ inches (57 cm.); at chin, 25¾ inches (65 cm.); neck, 20½ inches (52 cm.); chest, 51 inches (130 cm.); at navel, 52½ inches (133 cm.); at symphysis, 59 inches (150 cm.); thigh, at junction of middle and lower thirds, 21 inches (53 cm.); lower leg, 15 inches (38 cm.); circumference of humerus, 16½ inches (42 cm.); forearm, 13½ inches (34 cm.); wrist, 9½ inches (24 cm.).

CASE XXIII. FIG. 3.—NOTE SHORT, BROAD TEETH, WITH GOOD ALIGNMENT AND OCCLUSION, AND ABSENCE OF SEPARATION.

Regional.—Head: Head and face show marked obesity, extending from the temporal regions down, with a marked double chin. Cheeks very large and obese, supraclavicular fat pads uniting almost directly with the obesity of the cheeks. Ears normal in shape and size. Hair distribution of the head, eyebrows, and eyelids normal. Temporal arteries not visible or palpable. No compression tenderness over sinuses, muscle attachments, or nerve exits. *Ears* and *eyes:* negative. *Nose:* Straight, not retroussé, no marked indentation along the upper bridge, more of a pituitary type. Mucous membranes free from lesions; no obstruction of the nares. *Mouth:* Teeth all very straight, no overcrowding of the lower teeth, lower toothline almost perfect; nearly all the teeth present. Mucous membranes show congestion, very slight cyanosis, no lesions or pigmentation. Tongue very large, coated. Pharynx injected, tonsils enlarged. *Neck:* Marked obesity, folds extending from the maxilla down, supraclavicular fat pads very distinct. Neck short and thick. Thyroid not palpable, no pulsation of the arteries or veins, lymph-glands not palpable. *Chest:* Marked fat folds about the posterior portion of the occipital region and the neck posteriorly. Mammary glands large, fitting tight against the large abdomen, which comes to that height. Abdomen very tense and full in the sitting position with legs straight. Chest markedly increased in size, anterior-posterior diameter greater than lateral. Very few fat folds in the posterior portion of the chest at its junction with the abdomen. Slight abnormal distribution of hair about the lower lumbar region and about the posterior folds of the chest superiorly. Tactile fremitus equal, normal expansion fair, equal; hyperresonant percussion note throughout. No abnormal transmission of voice, whispered, or breath sounds; no râles, rubs, or other adventitious sounds in the lungs or pleuræ. *Heart:* Apex-beat not made out in the sitting position, not visible or palpable in the lying position. No diastolic shock, thrill, rub, or bruit palpable (on account of the obesity and the distention of the abdomen). Heart borders not made out definitely on percussion. (For the exact size, see the fluoroscopic report.) Very small area of cardiac dullness, extending two fingerbreadths to the left of the sternum. Sounds very distant, slightly increased in rate, regular. No murmurs, rubs, findings of disassociation or auricular fibrillation. *Abdomen:* Very much distended and enlarged, of the hanging type, walls exceedingly thick. No tenderness, soreness, increased resistance, or rigidity. Some dullness in the left flank, none in the right on percussion. Hernial openings closed. Abdominal organs difficult to make out on account of the size of the abdomen and the thickness of its walls; no abnormalities to physical examination.

LABORATORY FINDINGS.—*Urine.*—(*a*) Single specimen, color straw, specific gravity 1.018, reaction acid. Trace of albumin, few leukocytes and granular casts. Dextrose and erythrocytes, negative.

(*b*) Twenty-four-hour specimen, 1,000 c.c., color straw, specific gravity 1.020, reaction acid. Trace of albumin, few hyaline and granular casts. Dextrose, leukocytes, and erythrocytes negative.

Feces.—(*a*) Following blood-free diet, black, formed. Mucus, ova, and parasites negative. Pus and occult blood positive.

(*b*) Brown, formed. Mucus, ova, parasites, pus, and occult blood, negative.

Blood:

Erythrocytes	5,100,000
Leukocytes	10,800
Hemoglobin	105 per cent.
Wassermann	negative
Differential analysis:	
Neutrophilic leukocytes	45 per cent.
Eosinophilic leukocytes	1 " "
Large lymphocytes	2 " "
Small lymphocytes	50 " "
Mononuclears	2 " "

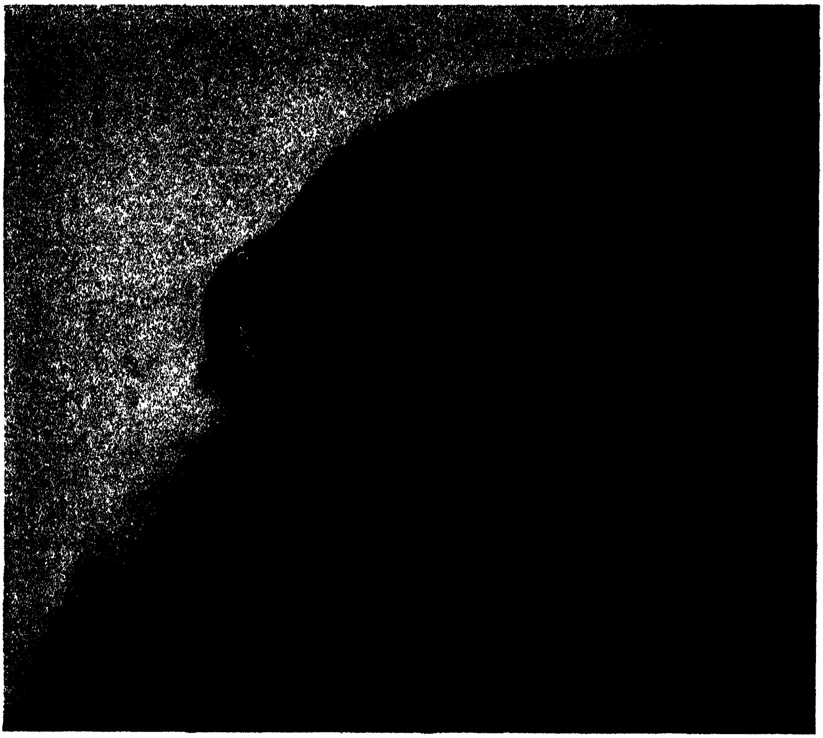
Blood-sugar:

(*a*) First specimen	0.052
(*b*) (Following ingestion of 300 grams (10½ ounces) glucose in twenty-four hours, and intramuscular injection of 1/1000 adrenalin)	0.088

SPECIAL EXAMINATIONS.—*Ophthalmic* (Dr. E. P. North).—"Lid fissure narrowed; ptosis, both lids. Vision—O. D. (right eye)—20/32. Vision—O. S. (left eye)— 20/32. Pupils equal, but react sluggishly to light and accommodation. Both external recti faulty. Field for form normal. Ophthalmoscope shows media clear; optic discs clear in outline, temporal pallor of both optic discs. Vessels engorged and tortuous, particularly veins. Color vision normal. In conclusion, eyes negative, with exception of ptosis of both lids and marked temporal pallor of both discs."

Roentgenogram of Head.—Sella turcica small. Anterior skull angle acute.

Diagnosis.—The diagnosis in this case is ***bilobar hypopituitarism, occurring in late adolescent life, of the aneoplastic type.*** Hypothyroidism unquestionably occurred as a late complication to the pituitarism. The diagnosis of pituitarism is based upon the following analysis. It is taken for granted that originally there probably was a hyperactivity of the anterior lobe present in this case. The unusual height of the individual; the large head; the large, straight, well-formed nose; the well-developed malar bones; the large hands and feet; and the well-developed and functionating gonads, would substantiate this reasoning. This unusual skeletal growth and the well-formed and active genital system were present without obesity or other evidence of decreased metabolism, until the patient had arrived at the age of over thirty. At that time he began gradually to take on weight, which persisted progressively until the time of observation, resulting in a gain of 200 pounds. The history states that this adiposity was first noticed particularly around the abdomen and hips, only in the past few years affecting the entire body. There was no decided change occurring in any other system until the age of thirty-four, when the obesity began to be more marked in the extremities, in the cervical region, and on the backs of the hands. It was at this age that the somnolence commenced. Coincident with the somnolence there occurred marked loss of libido. An explanation of these differences in the physical or hormonic signs probably would be, first, that at the age of about thirty, previous to which time the patient had had a slight hypersecretion of the anterior lobe, this began to change into exactly the opposite secretion or an inactivity of this lobe of the hypophysis. At the same time there occurred a gradually increasing insufficiency of the posterior lobe, which is accountable for the onset and the gradual progress of the obesity. The functions of both these lobes became more and more decidedly insufficient, until the age of thirty-eight, when there was an almost complete inactivity of the anterior lobe, as is evidenced by the complete loss of libido at that time. Coincident with this anterior lobe inactivity, combined with a progressively increasing insufficiency of the posterior lobe, there also occurred at the age of thirty-eight a marked secondary insufficiency of the thyroid. This combined insufficiency of the posterior lobe with the thyroid, is taken to date from the onset of the somnolence occurring at that time. The marked increase of somnolence during the past four years, until its extreme state of hibernation, when the patient



CASE XXIII. FIG. 4.—NOTE SMALL SELLA TURCICA.

could hardly be kept awake (the time of observation), is an indication of a combined increasing deficiency of both the posterior lobe of the hypophysis and the thyroid gland. Other symptoms indicating complications of a late hypothyroidism are the progressive disturbances of articulation, the dribbling salivation, and the increasing subdermal infiltration and padding about the backs of the hands and the neck. A continuation of the inactivity of the anterior lobe is shown by the continuous loss of libido and potentia during the past four years. Other clinical proof that the pituitarism was the primary lesion in this case, and the hypothyroidism only a late complication, is that of the reaction to therapy. It will be noted by referring to the Subsequent Course of the case and the reaction to treatment, that there was only a partial relief of the symptoms resulting from the unaided use of thyroid gland therapy. This relieved the patient to a marked degree from his somnolence, mental depression, inarticulate speech, dribbling salivation, and, to a slight extent, from the infiltration of the subdermal adipose tissue of the extremities, hands, and neck. After it was given to tolerance, that is, to the point at which the patient had evidence of hyperthyroidism, consisting of tachycardia, slight temperature, palpitation, general weakness, etc., without further producing loss of weight or amelioration of symptoms, it was taken for granted that the deficiency of secretion from the thyroid had been compensated. The patient, after the production of this effect, had lost only 48 pounds in weight and continued to complain of visual symptoms, some mental depression, and general incapacity from his enormous obesity. At this time posterior lobe pituitary extract was added to the thyroid treatment, producing an additional reduction in weight and a most decided further relief of the symptoms which had been present after the thyroid therapy had been given to tolerance.

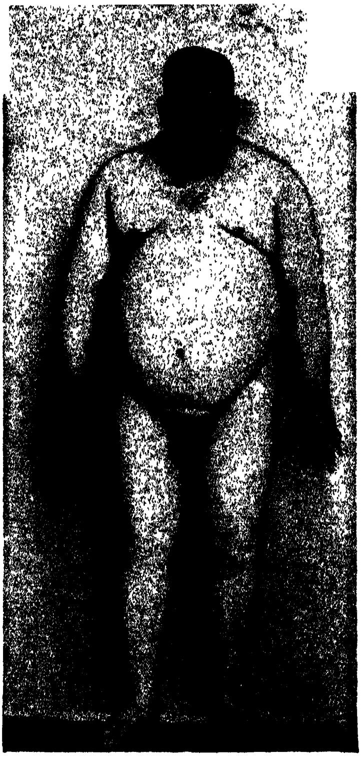
There were no focal signs referable either to the pituitary gland or to the thyroid indicative of anomalous secretion from either of these endocrinous organs. The roentgenogram of the head showed an absence of enlargement of the sella turcica, and the history and physical examination showed evidence of no intracranial pressure symptoms nor demonstrable changes in the thyroid gland.

If such changes were present, the thyroid would have been decreased in size; although occasionally it becomes enlarged, even though its secretion is below the normal in amount. The marked obesity of the neck was so extreme at the first examination that moderate enlargement of the thyroid would not have been discovered had it been present. The presence, however, of gross hormonic signs of both these glands, made the diagnosis in this case comparatively simple and easy. The original diagnosis was confirmed by the later effects of simple substitution treatment of a combination of the thyroid and the posterior lobe of the hypophysis, completely relieving every symptom and markedly decreasing the extreme abnormal hormonic signs referable to both of these glands. The laboratory examinations, consisting of the marked increase in sugar tolerance, the marked lymphocytosis, and the low blood-pressure, taken with the markedly slow pulse and the subnormal temperature, confirm the presence of inactivity of either one or both the thyroid and hypophyseal posterior lobe secretions.

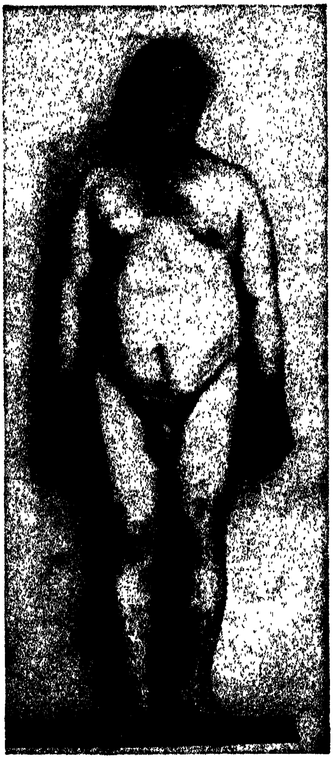
Complications, Sequelæ, and Associated Diseases.—There were no complications or sequelæ of this disease up to the time of observation. The marked somnolence or state of hibernation in which the patient was at this time might be considered a sequela. Yet it should be considered one of the symptoms produced by a decided deficiency of both the posterior lobe of the pituitary and the thyroid, occurring at the same time in the same individual. This is the type of case described in the lay press, of patients who sleep for an unusual length of time and can not be awakened by any sort of stimulus. Complete loss of libido and impotence might also be considered a sequela of this polyglandular insufficiency. It undoubtedly is more marked in the combined thyroid and posterior lobe hypophyseal insufficiency than it is in either one alone; yet it is really one of the hormonic symptoms that could be caused by either endocrinous gland. There were very few other diseases associated with this condition in this individual case. This is rather unusual, as it is just this type of late bilobar hypopituitarism which seems to be more susceptible to intercurrent infections.

Clinical Varieties.—The extreme, prolonged somnolence existing in this case is considered so specifically characteristic of this peculiar combination of endocrinous insufficiency that the writers have taken the liberty to attempt to designate it as a special clinical variety under the term, *pituitary hibernation.* Cushing and Goetsch, under the name of *hibernation of the pituitary body,* state that the changes in the hypophysis during the hibernation of certain animals are probably simply an inanition effect. The rapid growth of the body following periods of inanition may be due to the embryonic conditions to which the cells are reduced, but there is no evidence that such growth is due to any specific histological changes in the hypophysis or other ductless glands. Gemelli has found, in the albino rat, that after hibernation, the hypophysis, presumably awaking from a state of functional inactivity, shows an apparent cellular hyperplasia, with mitotic cell division. Rev. Hansemann found no interstitial cells of Leydig in the testicle of the same animal, during hibernation. When the dormant period had passed, they were so great in number that the testes on section resembled a sarcoma. Experiments on animals in which a partial hypophysectomy is done result constantly in the production of a lazy, somnolent animal, with marked tendency to sleep. Stewart has reported cases in which pathological drowsiness was a striking feature, and attributed it to an upward pressure upon the infundibulum. Normal or artificially produced sleep has been considered by some physiologists as a periodical functional inactivity of the hypophysis, and it is interesting to note the increasing literature on this subject relating to the possible effects of drugs upon the hypophysis as a cause for somnolence. The usual physiological explanation for natural sleep is that of anemia of the brain produced probably through vasomotor constriction from exhaustion.

Sleep or unconsciousness produced by anesthetic drugs, such as ether, etc., has never been easily explained. It is known that just previous to the stage of somnolence or unconsciousness during these anesthetics there is a period of excitation. The possibility of these volatile drugs producing a temporary inactivity of the endocrinous glands, resulting in periods of sleep, associated with complete loss of sensation and reflex control, has more recently been given consideration. As noted above, the long stages of hibernation which are naturally undergone by certain species of animals have been attributed by some investigators to a simple inactivity of the hypophysis. As has been shown by Gemelli, during this time there is also apparently a marked histological change in the interstitial cells of the gonads, consisting of an aplasia, which after hibernation changes into a hyperplasia of the interstitial cells of the gonads. These histological changes in both the gonads and the pituitary are markedly altered following this hibernation into the opposite state of



CASE XXIII. FIG. 5A.—NOTE MARKED OBESITY ABOUT HYPOGASTRIUM AND MONS, MAMMARY DEVELOPMENT, SPADE-LIKE HANDS, AND STUPID, APATHETIC EXPRESSION.



CASE XXIII. FIG. 5B.—SAME CASE (XXIII) AFTER TREATMENT. NOTE MARKED DECREASE IN OBESITY. LOSS OF APATHY, AND INCREASE IN ALERTNESS AND ERECTNESS OF POSITION.

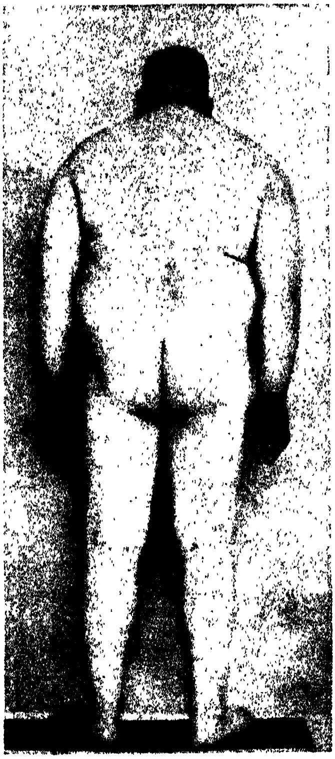
hyperplasia. General mental depression, tendency to torpidity, somnolence, and lack of concentration are also symptoms of simple thyroid insufficiency. The writers have never seen this extreme sign of hibernation, however, associated with the simple thyroid inactivity. They are inclined to believe that it is more than likely always due to a *posterior pituitary lobe insufficiency associated with a thyroid insufficiency,* and that neither of these glands *alone* is liable to produce the extreme, prolonged state of somnolence which could be designated as a clinical type of hibernation.

Treatment.—The therapy of the case and the reaction to treatment given were as shown in Table 5.

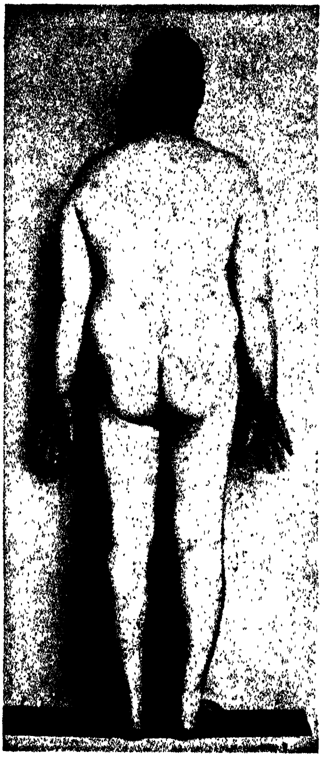
TABLE 5. SUBSEQUENT COURSE AND THERAPY

Date	*Treatment*	*Reaction*
April 4–April 14	Thyroid gland gr. ii t. i. d.	Patient's diurnal somnolence and nocturnal insomnia and restlessness improved rather decidedly, so that he was able to keep awake during the day and to sleep comfortably during the night. During this time he lost on an average 2 pounds daily for the first week. After that time his weight remained stationary for four days. Temperature subnormal and pulse below 90.
April 14–May 14	Thyroid gland gr. iv t. i. d.	Patient lost weight progressively, from 1 to 2 pounds daily for over two weeks, on this dosage, and then his weight remained stationary. Further continuation of the treatment for a week finally increased the pulse-rate from 90 to 114.
May 14–May 19	Thyroid discontinued. Pituitrin ♏ viii subcutaneously given daily.	After each injection the patient would feel slightly nauseated for ten minutes. Within four or five minutes after the hypodermic, severe abdominal cramp and colic would occur. Within eight to ten minutes, patient would have a large defecation. The pulse had returned to below 80. The temperature remained subnormal. Daily loss of weight, from 1 to 1½ pounds.
May 19–June 13	Thyroid gr. iii t. i. d. Pituitrin ♏ viii daily.	Reaction following pituitrin constantly present. Weight gradually decreased, averaging 1¼ pounds daily. Pulse remained below 92; temperature below 98.8° (37.1° C.) rarely reaching 98.6° F. (37° C.).
June 13–June 20	Pituitrin ♏ xii H daily. Thyroid gr. iv t. i. d.	General condition much improved. Weight again became stationary for three days. Temperature subnormal; pulse below 90. Reaction to pituitrin less marked.
June 20–June 28	Thyroid gr. v t. i. d. Pituitrin 1 c.c. H subcutaneously.	General reaction negative. Average decrease in weight of ¼ to ½ pound daily. Intestinal reaction to pituitrin same.
June 28	Thyroid gr. v t. i. d. Pituitrin 1.3 c.c. daily.	Intestinal reaction to pituitrin slightly present. No general reaction. Loss of weight to present time increased to 1 pound daily.

REËXAMINATION (June 21, 1918).—*General.*—Marked change in make-up of the individual, somnolence entirely gone, intelligence and concentration present, speech very fluent. There is now no tendency to torpidity or sleep; the head is very erect. Very marked change in the amount of obesity. The large fat pads about the neck, both anteriorly and posteriorly, are greatly reduced. Abdomen very much smaller. Marked difference in padding of the backs of the hands and feet. Fingers now have tendency to tapering at the tips. Skin much less thick and infiltrated, although some evidence of thickening still present. Skin very loose, relaxed, can be raised from the superficial structures. Skin very moist, patient perspiring very decidedly over the entire body, without exertion. Skin on the backs of the hands against the bones, absolutely no padding, interosseous spaces visible at the bases of the phalanges. Skin on the dorsa of the feet also free from cushions or padding. No marked change in the distribution of hair. Character of the hair on the head is changed, not nearly so coarse or uncontrollable as previous to treatment. (Hair at that time could not be combed down, now lies rather flat.) Skin has reassumed a normal pink color, which is particularly noticeable on the exposed surfaces. Nails change in color halfway to the matrix to a deeper pink. This portion of the nail is increased in thickness, the outer half of the nail, toward the tip, being thinner, more fragile and serrated. Toenails have marked transverse ridge halfway to the tip. Transverse ridge on the fingernails not so marked as on the toes. Some fat folds around the posterior portion of the chest and abdomen still present, but folds about the neck have almost completely disappeared. Abdomen, as shown by the measurements, much reduced in size. Pulse increased in



CASE XXIII. FIG. 6A.—POSTERIOR VIEW. NOTE OBESITY AND POSTURE.



CASE XXIII. FIG. 6B.—NOTE DECREASE IN OBESITY AND CHANGE IN POSTURE AFTER TREATMENT.

rate. Mentality improved more than any other hormonic sign. Blood-pressure—systolic 135, diastolic 92.

Regional.—No changes from the previous examination, except marked change in the character of the hair.

Summary Effect of Treatment

	March 3, 1918	July 1, 1918
Weight	346 pounds	274½ pounds
Blood-pressure	158 (systolic)	135
Measurements:		
Chin	25¾ in. (65 cm.)	22 in. (56 cm.)
Neck	20½ " (52 ")	18¼ " (46 ")
Chest	51 " (130 ")	44½ " (113 ")
Navel	52½ " (133 ")	46 " (117 ")
Hips	59 " (150 ")	43½ " (110 ")
Thigh (at junction of upper and middle thirds)	21 in. (53 cm.)	21 in. (53 cm.)
Calf	15 " (38 ")	14½ " (37 ")
Humerus	16½ " (42 ")	12¾ " (32 ")
Forearm	13½ " (34 ")	10¼ " (26 ")
Wrist	9½ " (24 ")	7¼ " (18 ")

It will be noted that the most important effect upon the hormonic signs was in the loss of weight of 71½ pounds and in the circumference measurements (1) of the hip (15½ inches, 40 cm.); (2) of the chest (6½ inches, 17 cm.); and (3) of the neck (2¼ inches, 6 cm.).

The improvement of the patient's mentality, being entirely relieved of the diurnal somnolence and nocturnal insomnia, was quite decided. This resulted entirely from the use of **thyroid treatment.** This thyroid treatment was effective for the first two weeks of the patient's observation, during which time he lost 34 pounds. It will be noted that after this his weight remained stationary, and exhibition of large doses of thyroid began to produce symptoms of hyperthyroidism, consisting of tachycardia, marked weakness, and nervousness, requiring the withdrawal of this treatment. After the maximum effect had been procured from thyroid medication given to tolerance, it will also be noted that a further reduction in weight and improvement of all the hormonic signs was accomplished by the addition (to this thyroid treatment) of **pituitrin** (extract of the pituitary posterior lobe). After the ultimate effects have been procured with the combined thyroid and posterior pituitary treatment, **anterior lobe pituitary** extract should be added as a therapeutic agent. This may possibly produce an additional improvement, particularly referable to the restoration of the function of the gonads, *i. e.,* relief of impotence.

Prognosis.—The prognosis, both as to recovery and as to relief of symptoms, in this case is most favorable. This unusually encouraging prognosis for hypophyseal disease is based upon the fact, first, that there is no neoplastic involvement of the pituitary, and second, that all the hormonic signs and symptoms have been completely relieved by therapy. The prognosis with regard to the restoration of the functions of the two glands involved in this case is not so favorable. It is more than likely that the patient will have to take a certain amount of treatment indefinitely in order to prevent recurrence of the original symptoms.

Pathology.—The pathology in this case corresponds to that of the bilobar hypopituitarisms free from pituitary tumor. The histological changes in the glands have been frequently referred to in previous chapters. The pathological changes in other tissues of the body have also frequently been reviewed in various preceding chapters. This case does not differ particularly from those of simple insufficiency of both lobes of the hypophysis, except in the fact that it has added to its pathology that of the hormonic tissue changes of the secondary insufficiency of the thyroid.

LITERATURE

Allen, F. M., Hulton, F., and Taylor, A. E. Glycosuria and Diabetes. Jour. Biol. and Chem., Cambridge, 1913, xxv, 175.

Anton. Vier Vorträge über Entwicklungsstörung beim Kind. Berlin, 1908.

——— Reiner Psychoinfantilismus. Forens. Psychiatrie, 1910, 2.

Arnold, J. Further Studies in Connection with the Question of Acromegaly. (Weitere Beiträge zur Akromegaliefrage.) Virchows Arch. f. path. Anat., 1894, cxxxv, 1-78.

Aschner, B. Function of the Hypophysis. (Ueber die Funktion der Hypophyse.) Arch. f. d. ges. Physiol., 1910, xxi, 160.

Aschner and Goetsch. The Relation of the Pituitary Gland to the Female Generative Organs. Surg., Gynec., and Obst., xxv, 230-233.

Aub, J. C., and Du Bois, E. F. Clinical Calorimetry, Nineteenth Paper. The Basal Metabolism of Old Men. Arch. Int. Med., Chicago, 1917, xix, 823-831.

Bab, H. Die Hypophyse als Regulator der Diurese und des spezifischen Gewichts des Harnes. Münch. med. Wchnschr., 1916, lxiii, 1685, 1721, 1758.

Babonneux, L., and Poisseau, G. Some Cases of Infantile Obesity. (Sur quelques cas d'obesité infantile.) Gaz d. hôp., 1910, lxxxiii, 1431-1435.

Bartels, M. Squamous Epithelial Tumors in the Region of the Hypophysis. (Ueber Plattenepithelgeschwülste der Hypophysengegend (des Infundibulums.) Ztschr. f. Augenheilk., 1906, xvi, 407; 530.

——— The Relation of the Changes in the Region of the Hypophysis to Physical Deformities and Disturbances of the Genital Organs. (Ueber die Beziehungen von Veränderungen der Hypophysengegend zu Misswachstum and Genitalstörungen [Dystrophia adiposogenitalis]). München. med. Wchnschr., 1908, lv, 201.

The Question of Disturbances of the Hypophysis. (Zur Frage der Hypophysisstörungen.) Klin. Monatsbl. f. Augenheilk., Lima, Peru, 1914, lii, 604.

Bauer, A. Infantilisme et chétivisme. Presse méd., Paris, Dec. 4, 1909, 870-872.

Bell, W. B. The Pituitary, 1919, Part I, p. 79: Incidence—The Physiology of the Pituitary.

Bell, W. B. *Ibid.*, p. 237; Incidence—Hypopituitarism Occurring before Puberty.

——— *Ibid.*, pp. 158-177; Incidence—Effect of Posterior Lobe Secretion upon the Gonads.

Benda, C. Normal and Pathological Histology of the Human Hypophysis Cerebri. (Beiträge zur normalen und pathologischen Histologie der menschlichen Hypophysis cerebri.) Berl. klin. Wchnschr., 1900, xxxvii, 1205-1210.

Biedl, A. Internal Secretion. (Innere Sekretion.) Berlin, 1910.

——— Innere Sekretion. Urban u. Schwarzenberg, Wien u. Berlin, 1913, 534 p., 8 pl.; 694 p., 6 pl.

Bramwell, B. Infantilism: No Apparent Cause. Clin. Stud., 1908, vi, 389-392.

Brissaud, E. L'infantilisme vraie. N. iconog. de la Salpêtrière (Paris), 1917, xx, 1-17.

Brissaud, E., and Meige, H. Gigantisme et acromégalie. Rev. Scient., 1895, iii, 330-336.

——— *Ibid.*, Type infantile du gigantisme. N. iconog. de la Salpêtrière, Paris, 1904, xvii, 165-172; Rev. neurol., 1904, xii, 191-194.

Courtellemont, V. Tumors of the Pituitary Body. (Des tumeurs du corps pituitaire.) Rev. neurol., 1911, xix, 261-270. Bull. méd., 1911, 699.

Crowe, Cushing and Homans. The Pituitary Body and Its Disorders, 1910, p. 13, and note at bottom of page. Incidence—anterior lobe insufficiency producing obesity, etc.

Cruetzfeldt, H. G. Normal and Pathological Anatomy of the Hypophysis Cerebri in Man. (Ein Beitrag zur normalen und pathologischen Anatomie der Hypophysis cerebri des Menschen.) Jahrb. d. Hamb. Staatskrankenanst., 1909, xiii, 273-294.

Cummings, R., and Piness, G. Arch. Int. Med., 1917, xix, 777; Jour. Am. Med. Assn., April 20, 1918, lxx, No. 16, 1132.

Cushing, H. The Pituitary Body and Its Disorders, Edition 1910, p. 231: Incidence—Trauma.

——— *Ibid.*, p. 15: Incidence—Thermic Reaction to Anterior Lobe Preparations.

——— *Ibid.*, p. 25: Incidence—Classification of states of Dyspituitarism.

——— *Ibid.*, p. 95: Case XIV. Incidence—Hypophyseal Struma.

——— *Ibid.*, Case XXXVII, p. 186; Incidence—Adult Hypopituitarism, Suggestive Neighborhood Symptoms for Which Decompression Sellar Operation Is Done.

——— *Ibid.*, p. 239: Incidence—Size of the Normal Sella Turcica.

——— *Ibid.*, p. 263: Case XLVIII. Gumma of the Hypophysis.

——— *Ibid.*, p. 277: Incidence—The Histological Change in the Gonads Present in Hypopituitarism.

——— *Ibid.*, p. 291: Incidence—Summary of Pathology and Histology of Hypophyseal Tumor.

——— *Ibid.*, p. 279: Incidence—Retention of the Ovulation and Conception in Marked Anterior Lobe Insufficiencies.

——— *Ibid.*, p. 274: Incidence—Relation of Hypophyseal Insufficiency to Epilepsy.

——— The Functions of the Pituitary Body. Am. Jour. Med. Sc., Philadelphia and New York, 1910, xxxix, 473-484.

——— Dyspituitarism. Harvey Lecture, Philadelphia and London, 1911, 31-46.

——— Shattuck Lecture Concerning Diabetes Insipidus and the Polyurias of Hypophyseal Origin. Communications Med. Soc., Boston, 1913, xxiv, Part I, 23-49. L Diag.

——— Address on Surgery; on Re-alinements in Greater Medicine, Their Effect upon Surgery and the Influence of Surgery upon Them. Brit. Med. Jour., London, 1913, ii, 290-297.

Cushing, H. Partial Hypophysectomy for Acromegaly; with Remarks on the Function of the Hypophysis. Ann. Surg., Philadelphia, 1909, i, 1002-1017. 3 pl.

Cushing and Aschner. The Pituitary Body and Its Disorders, 1910, p. 7: Incidence—Polyuria and Libido Following Experimental Hypopituitarism.

Cushing and Goetsch. Concerning the Secretion of the Infundibular Lobe of the Pituitary Body and Its Presence in the Cerebrospinal Fluid. Am. Jour. Physiol., 1910, xxvii, 60-86.

———— Hibernation and the Pituitary Body. Abstract Proc. Soc. Exper. Biol. and Med., 1913-14, xi, p. 25.

——— The Pars Anterior and Its Relation to the Reproductive Glands. Abstr. Proc. Soc. Exper. Biol. and Med., 1913-14, xi, 26.

——— Hibernation and the Pituitary Body. Jour. Exper. Med., 1915, xxii, 25-47.

Du Bois, D., and E. F. Clinical Calorimetry; Tenth Paper. A Formula to Estimate the Approximate Surface Area if Height and Weight be Known. Arch. Int. Med., Chicago, 1916, xvii, 836-871.

Eiselsberg, F. (Discussion.) Wien. klin. Wchnschr., 1909, xxii.

Erdheim, J. Normal and Pathological Histology of the Thyroid, Parathyroid and Hypophysis. (Zur normalen und pathologischen Histologie der Glandula thyreoidea, parathyreoidea und hypophysea.) Beitr. z. path. Anat. u. z. allg. Path., 1903, xxxiii, 158-236.

———— Eosinophil and Basophil Adenoma of the Hypophysis. (Ueber das eosinophile und basophile Hypophysenadenom.) Frankf. Ztschr. f. Path., 1910, iv, 70-86.

Erdheim and Stumme. The Changes in the Hypophysis during Pregnancy. (Ueber die Schwangerschaftsveränderung der Hypophyse.) Beitr. z. path. Anat. u. z. allg. Path., 1909, xlvi, 1-132.

Falta and Meyers. The Ductless Glandular Diseases, 2nd Edition, p. 471: Incidence—Thermic Reaction of Pituitrin, in Glandular Injections.

———— The Ductless Glandular Diseases, 1915, p. 298: Incidence—Production of Thermic Reaction with Injection of Anterior Lobe Substance.

Fischer, B. Ref. of Falta and Meyers, The Ductless Glandular Diseases, 1915, p. 317: Incidence—Production of Obesity due to the Posterior Lobe.

———— Hypophysis, Akromegalie und Fettsucht. Wiesbaden, J. F. Bergmann, 1910.

Frankl-Hochwart, V. Diagnosis of Tumors of the Hypophysis without Acromegaly. (Die Diagnostik der Hypophysentumoren ohne Akromegalie.) 16 Intern. Med. Kongr., Budapest, 1909.

Fröhlich, A. A Case of Tumor of the Hypophysis Cerebri without Acromegaly. (Ein Fall von Tumor der Hypophysis cerebri ohne Akromegalie.) Wien. klin. Rundschau, 1901, xv, 883-906.

Gemelli, A. Recent Contribution on the Physiology of Hypophysis Dystrophy. (Ulterio contributo alla fisiologia dell ipofisi.) Folio Neuro-biologica, 1908, ii, 167-196.

Goetsch, E. The Influence of Pituitary Feeding upon Growth and Sexual Development. Bull. Johns Hopkins Hosp., xxvii, No. 300, Feb., 1916.

Goetsch, E., Cushing, H., and Jacobson, C. Carbohydrate Tolerance and the Posterior Lobe of the Hypophysis Cerebri. Bull. Johns Hopkins Hosp., 1911, xxii, 165-190.

Goldstein, K. Serous Meningitis in Diseases of the Hypophysis. (Meningitis serosa unter dem Bilde hypophysärer Erkrankung. Zur Differentialdiagnose des Tumor cerebri und Meningitis serosa.) Arch. f. Psychiat., 1910, xxvii, 15-17.

Graves, W. W. Ueber Lückenbildung zwischen den einzelnen Zähnen; ein frühdiagnostisches und bisher wenig bekanntes Zeichen der Akromegalie. Monatsschr. f. Psych. u. Neurol., 1904, xvi, Heft 1.

Hansemann. The Disorders of the Pituitary Body. Cushing, 1910, p. 233 (Note): Incidence—Hypoplasia in Leydig Cells in Albino Rat during Hibernation, etc.

Hopkins, A. H. Am. Jour. Med. Sc., 1915, 149-254.

Horseley, V. Functional Nervous Disorders Due to Loss of Thyroid Gland and Pituitary Body. Lancet, London, 1886, i, 5.

Howell. The Physiological Effects of Extracts of the Hypophysis Cerebri and Infundibular Body. Jour. Exper. Med., 1898, iii, 245-258.

Jackson, C. M. Effects of Inanition and Refeeding upon the Growth and Structure of the Hypophysis in the Albino Rat. Am. Jour. Anat., xxi, No. 2, 321.

Jacobson, A. T. B. Biochem. Ztschr., 1913, lvi, 471.

Janney, Goodhart and Isaacson. The Endocrine Origin of Muscular Dystrophy. Arch. Int. Med., xxi, No. 2, p. 188.

Janney and Isaacson. Blood Sugar Tolerance Test. Jour. Am. Med. Assn., lxx, No. 16, April 20, 1918, 1131.

Kumell. Growths of the Pituitary Gland. München. med. Wchnschr., 1911, 1293. (Zur Kenntnis der Geschwülste der Hypophysengegend.)

Levi, E. A Study of Infantilism of the Lorain Type. (Contribution à l'étude de l'infantilisme du type Lorain.) N. iconog. de la Salpêtrière, 1908, xxi, 297 and 421.

——— The Question of Infantilisms. (Encore sur la question des infantilismes.) N. iconog. de la Salpêtrière, 1910, xxiii.

Lewis, D. D. Hyperplasia of the Chromophile Cells of the Hypophysis as the Cause of Acromegaly, with Report of a Case. Bull. Johns Hopkins Hosp., 1905, xvi, 157-164.

Lorain. Lettre preface à la Thèse de Faneau de la Cour, 1871.

Marburg, O. Adiposis Cerebralis. (Die Adipositas cerebralis.) Wien. med. Wchnschr., 1908, lviii, 2617-2622. *Also,* Deutsch. Ztschr. f. Nervenh., 1908-9, xxxvi, 114-121.

——— Normal and Pathological Histology of the Pituitary Body—Adiposis Cerebralis. (Zur Kenntnis der normalen und pathologischen Histologie der Zirbeldrüse. Die Adipositas cerebralis. Arb. a. d. Inst. f. Anat. u. Physiol. d. Centralnervensyst. an d. Wien. Univ., 1909, xvii, 217-279.

Marie, P. Acromegaly. (L'acromegalie.) N. iconog. de la Salpêtrière, 1888, i, 173, 229; *Ibid.,* 1889, ii, 45, 96, 139, 188, 224, 327; Abstract. Bull. Med., 1889, iii. 1579-1581; Le progrès méd., 1889, ix, 189-192; Brain, 1889-90, xii, 59-81.

Marinesco and Goldstein. Two Cases of Hydrocephalus with General Adiposity. (Deux cas d'hydrocephalie avec adipose generalisée.) N. iconog. de la Salpêtrière, 1909, xxii, 628-649.

McCrudden and Sargent. Chemical Changes in the Blood and Urine in Progressive Muscular Dystrophy, Progressive Muscular Atrophy and Myasthenia Gravis. Arch. Int. Med., 1918, xxi, No. 2, 252.

Meige and Allard. Two Cases of Infantilism: Myxedematous Infantilism and Lorain's Infantilism. (Deux Infantiles: Infantilisme myxedeme et Infantilisme de Lorain.)

Minkowski. A Case of Acromegaly. (Ueber einen Fall von Akromegalie.) Berl. klin. Wchnschr., 1887, p. 371.

Oliver and Schafer. On the Physiological Action of Extracts of the Pituitary Body. Jour. Physiol., 1895, xviii, 277.

Paltauf, A. The Growth of Dwarfs. (Ueber den Zwergwuchs.) Hölder, Wien, 1891.

Paulesco. Hypophysis of the Brain. (L'hypophyse du cerveau.) I. Physiologie, Vigo Frères, Paris, 1908, 148.

Pemberton, R., and Sweet, J. E. Further Studies on the Influence of the Ductless Glands on the Pancreas. Arch. Int. Med., Chicago, 1910, v, 466-481.

PONFICK, E. Myxedema and Hypophysis. (Myxedem und Hypophysis.) Ztschr. f. klin. Med., 1899, xxxviii, 1-25.

RENNIE. Endothelioma of the Pituitary Gland with Infantilism. Brit. Med. Jour., June, 1912, 150.

ROHDENBURG, G. L., BERNHARD, A., AND KREHBIEL, O. A Study of Sugar Mobilization Based upon 228 Human Cases. Am. Jour. Med. Sc., Phila., 1920, clix, 577-586.

ROUSSY, G., AND CLUNET, J. Tumors of the Anterior Lobe of the Hypophysis. Histological Classification. (Tumeurs du lobe anterieur de l'hypophyse. Essai de classification histologique.) Rev. neurol., 1911, xix, 313-320.

SANSUM, W. D., AND WOODYATT, R. T. Jour. Biol. Chem., 1916, 24-343. Jour. Am. Med. Assn., lxx, No. 16, April 20, 1918.

SCHAEFER AND VINCENT. Jour. Physiol., 1899, xxv, 87.

SCHAFER AND HERRING. The Action of Pituitary Extracts upon the Kidney. Phil. Tr., London, 1906, 1, 29. Abstr. in Proc. Roy. Soc., London, 1905-6, Ser. B., lxxvii, 271.

SCHAFER. The Action of Pituitary Extracts Upon the Kidney. Abstract Proc. Roy. Soc., London, 1905-1906, lxxvii, 271.

STEWART. Four Cases of Tumor in the Region of the Hypophysis Cerebri. Rev. neurol. and psychiat., 1909, vii, 225-241.

TANDLER, J. Investigations of the Skopzen. (Untersuchungen an Skopzen.) Wien. klin. Wchnschr., 1908, 277.

TANDLER AND GROSZ. The Effect of Castration on the Organisms. (Einfluss der Kastration auf den Organismus.) Wien. klin. Wchnschr., 1907, xx, 1596.

THOMSON, ST. CLAIR. The Cerebrospinal Fluid: Its Spontaneous Escape from the Nose. Cassell & Co., London, 1899.

VEST, C. W. Relation of the Glands of Internal Secretion to the Female Pelvic Organs. Bull. Med. Chir. Fac. Maryland, 1917, ix, 102-107.

WILDER, R. M., AND SANSUM, W. D. Glycose Tolerance in Health and Disease. Arch. Int. Med., Feb., 1917, 311; Jour. Am. Med. Assn., lxx, No. 16, April 20, 1918.

PART II

HYPERPITUITARISM

(*Hyperphysopathies*)

Gigantism, p. 607—Acromegaly, p. 623—Pituitary polyuria (Diabetes insipidus), p. 641—Pituitary glycosuria, p. 659—Pre-adolescent, bilobar variety, p. 667—Acromegaly, Polyuria and Glycosuria, p. 675

SECTION 11

GIGANTISM (EUNUCHOID)

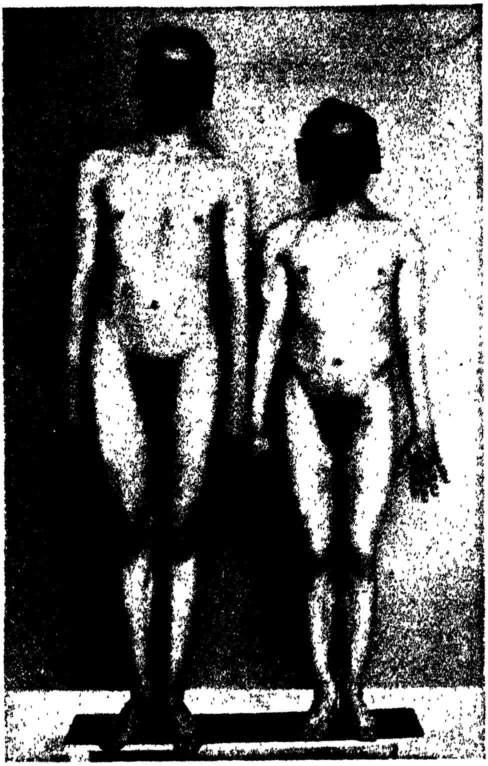
(*Anterior Lobe Hyperpituitarism, Pre-adolescent, Aneoplastic Type*)

Etiology.—The etiology in this case is undoubtedly one of heredity. Nearly all of these cases come from families which have gigantism present in at least one, or a number of generations. Acute infections, trauma, and the normal physiological changes of puberty and pregnancy are responsible causes for some of these cases. Launois and Roy reported a eunuchoid giant whose sudden and unusual growth commenced after an attack of typhoid fever. This infection, in this as well as in hypopituitarism, is undoubtedly one of the most prevalent predisposing causes. Trauma is not so frequently related to these hypersecretions as it is to the inactivities reported in previous sections. Pregnancy is much less liable to cause gigantism than to be productive of acromegaly. On the other hand, gigantism occurs more frequently following puberty than following pregnancy. This, of course, is due to the ages, relative to epiphyseal ossification, at which these two physiological changes occur.

Symptomatology.—History.—Case XXIV.—Mr. B. F. W., student, aged twenty, January, 1918.

The following patient, described as a eunuchoid giant, extended to the writers the privilege of making the following observations. He gave a negative history as to present complaints. He was leading the active life of a university student, and had been entirely free from illness of any kind since childhood. He was not especially active physically, having never been interested in sports or college athletics. On account of his physical development, he had been frequently solicited to join the athletic teams of the university, but had always declined. His progress through the university courses had been that of about the average student. His nervous stability was not up to the normal. He admitted that, contrary to the expectation derived from his physical development, he was naturally reserved, with a tendency to apprehension and nervousness, which was difficult to control under trial or stress.

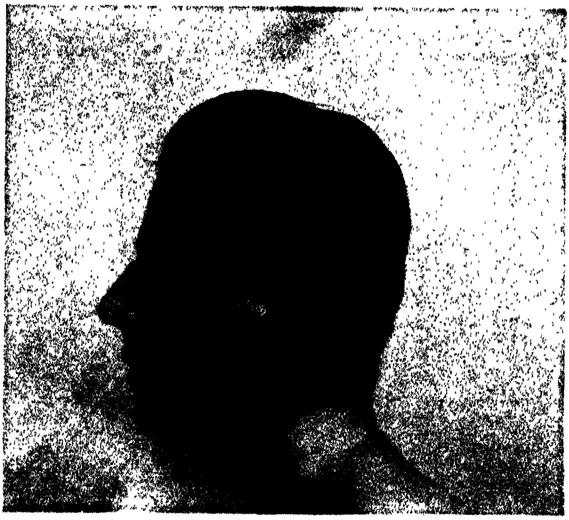
During childhood he had had the ordinary children's diseases, without complication or sequela. He *had never had typhoid fever or any severe injury.*



CASE XXIV. FIG. 1.—NOTE REMARKABLE HEIGHT (6 ft. 7 in.) AS COMPARED WITH NORMALLY-SIZED MALE OF CORRESPONDING AGE, EXTREME LENGTH OF LONG BONES, LARGE HANDS, WITH LONG FINGERS AND ABSENCE OF SPADE-LIKE CHARACTER, AND ATYPICAL DISTRIBUTION OF PUBIC HAIR.

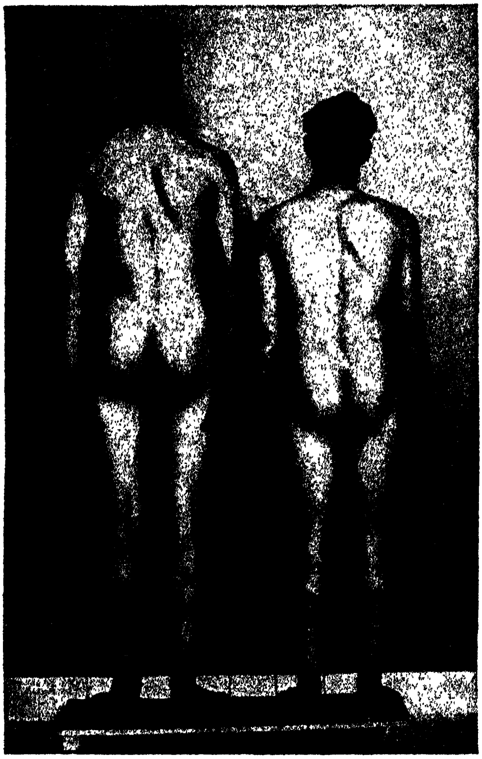
His family history is that of an *ancestry of a number of giants on the male side, for two generations.* One *living brother* is a *typical acromegalic giant.*

EXAMINATION.—*General.—Well proportioned eunuchoid giant stature.* Height, 6 feet 7 inches (201 cm.). Weight, 184 pounds. Measurements: From *vertex to symphysis, 35* inches (*89* cm.); from *symphysis to soles* of feet, *44 inches* (*112* cm.); length of bridge of nose, 2½ inches (6.3 cm.); humerus, 15 inches (38 cm.); forearm, 12 inches (30 cm.); femur, 21 inches (53 cm.); lower leg, 20 inches (51 cm.); circumference of head, 22½ inches (57 cm.); neck, 15 inches (38 cm.). *Size of glove, No. 8½; size of shoe, No. 10½; size of hat, 7¾.* Typical head, with classical pituitary nose and chin. Hands large, well proportioned; fingers long, wide, ends *not spadelike.* Feet of the same character. *Body,* with exception of *upper* and *lower* lengths, *well proportioned,* without obesity. Concavity over the lower portion of the sternum, producing slight congenital deformity, edges of the costal margins very close together. *No abnormal distribution of hair:* pubic hairline very straight, practically no hair on the abdomen or chest, no excessive amount on the extremities, very small amount in the axillæ. *No abnormal pigmentation,* skin lesions, or scars. No edema or dyspnea. Cyanosis of the hands and feet. Marked perspiration of the feet. *Temperament psychoneurotic,* fairly well controlled. Color of the rest of the skin good, of a normal pink. Pulse, moderately rapid, regular, equal, symmetrical, moderate volume and tension, rhythm good to 50. Pulse rate, 104.



CASE XXIV. FIG. 2.—NOTE LARGE, WELL-FORMED HEAD, PROMINENCE OF BONY MARKINGS, AND PITUITARY TYPE OF NOSE AND CHIN.

Regional.—Head: Large, well formed, bony markings unusually prominent. Ears symmetrically located, well proportioned in size, color good. *Hair distribution on the face considerably decreased;* eyebrows, eyelashes, and hair on the scalp normal. No anterior-posterior or lateral compression symptoms in the head. No localized pain or tenderness over the sinuses, muscle attachments, mastoids, or nerve exits. *Eyes:* Pupils equal, react to light and accommodation. No nystagmus on extreme divergence or convergence. *Eyes rather deep-set,* palpebral slits equal. Eye-muscle intact, no lagophthalmos or other thyroid eye signs. Scleræ free from pigment. *Nose: Unusually well developed, nares rather large,* equal. Septum straight, hypertrophy of the inferior turbinate bones. *Mouth:* Lips and mucous membranes normal, free from lesions and pigmentations. Teeth very straight, slight *separation of the upper incisors,* no overcrowding of the teeth, *number filled.* Tongue clean, pharynx injected, tonsils reach the pillars. *Neck: Thyroid slightly enlarged.* Veins prominent, but not pulsating, carotid pulsation not distinctly marked. Lymph-nodes not palpable. *Chest:* Deformity as noted above. Expansion fair, equal; tactile fremitus equal, symmetrical; percussion note of normal resonance throughout. No râles, rubs, or other



CASE XXIV. FIG. 3.—POSTERIOR VIEW AS COMPARED WITH NORMAL, SHOWING STRIKING INCREASE IN LENGTH OF LONG BONES.

adventitious sounds in the lungs or pleuræ; normal transmission of voice, breath, and whispered sounds. *Heart:* Apex-beat, *in the fifth interspace, within the nipple line.* Impulses present in the third and fourth interspaces, between this and the sternum. No diastolic shock, thrill, rub, or bruit palpable. *Marked impulse palpable over the entire precordia.* Slight impulse in the epigastrium, very slight one in the jugulum. Sounds, apex—slow, pure, regular, no murmurs. *Over pulmonic area—very decided, loud systolic murmur, which disappears during the second and third phases of deep inspiration. Accentuation of the second pulmonic tone,* but no thrill. Over aortic area—pure first tone, no accentuation of the second. *Marked "tit-tat" phenomenon over the gladiolus. Pulsations between the ribs, in the third, fourth, and fifth interspaces, which disappear on taking a deep breath* (raising sternum from heart and vessels). No abnormal signs over the large vessels of the chest on percussion or auscultation. Large vessels of the neck normal. No signs of disassociation or auricular fibrillation. *Abdomen:* Wide, broad, apparently short, on account of the very acute angle of the costal arch. No soreness, tenderness, or rigidity, but slight voluntary increased resistance. No tumefactions or dullness, including deep in the flanks. Hernial openings closed. *Spleen:* Not enlarged to palpation or percussion. *Liver:* Dullness four fingerbreadths above the costal arch, liver not percussible or palpable below the costal arch. Gall-bladder region free from tenderness and tumefaction. *Kidneys:* Not palpable. *Stomach:* Tympany four fingerbreadths above the costal arch. No tumefaction, peristalsis, or splashing sound. *Colon:* Cecum and ascending colon not palpable; transverse and descending colons, the same. *Genitalia:* Normal in size. Testicles, epididymi, scrotal contents, and penis negative. *Rectal:* Hemorrhoidal veins not enlarged. Prostate normal in size. Seminal vesicles not palpable. *Extremities:* Long bones unusually well developed (see measurements above). No joint or bone symptoms. No edemas or varicosities. *Reflexes:* Ankle clonus negative. Babinsky, Chaddock, Gordon, Oppenheim, negative. Patellars, Achilles, present, equal. Cremasterics, abdominals, pectorals, present, equal. Forearm, radio-ulnar, biceps, triceps, present, equal. Jaw jerk present, Chvostek negative.

LABORATORY FINDINGS:

Blood:

Wassermann	negative
Leukocytes	slightly increased (smear)

SPECIAL EXAMINATIONS.—*Roentgenogram of Skull.—Sella turcica normal in size,* deep; posterior clinoid process made out distinctly. Sinuses, sphenoid and frontal, very large. No abnormal detail in the remainder of the skull.

Diagnosis.—The diagnosis in this case is *hyperpituitarism, anterior lobe overactivity, occurring in pre-adolescent life, of the aneoplastic type.* Clinically, this case would be grouped with the *eunuchoid* type of giants. The history demonstrates the *absence* of constitutional symptoms resulting from the overactivity of the anterior lobe of the pituitary gland, which was present during the age of the development of the long bones. The overactivity of the anterior lobe is demonstrated by the overgrowth of all the bones and the *hyperplasia* of the genital system. That this overactivity occurred before the closure of the epiphyseal junctures is proven by the extreme development of the long bones, as shown in the *height* and the *individual measurements* of these bones. Hypersecretion of the anterior lobe of the hypophysis, however, is not limited in its hormonic effects merely to the *long* bones. The head and pelvis, made up largely of flat bones, and the hands and feet, with bones both flat and short, are as much affected, during pre-adolescence, by the "hormone of growth" from this lobe as are the long bones. This is shown by the size of the head itself, the circumference being 1-1½ inches (2.5-4 cm.) larger than the normal, and a hat size of 7¾. The size of the hat in gigantism is usually above 7½. All the pneumonic cavities in the skull are decidedly enlarged. The face is usually so well proportioned, and the individual parts so classically placed, that its increase in size is not noticeable. The large, straight-bridged nose, with the symmetrical nares, and the well-formed maxillæ, containing the large, well-enameled and perfectly set teeth, are characteristic signs of early increased secretion of the anterior lobe. The hand, as is shown in this case, is very characteristic. It has been designated by the French, the *"type en longe."* This is due to the *long, wide fingers,* which *overcome* the tendency to *disproportion produced by the width of the wrist.* This hand contrasts very strikingly with the extremely *small, pudgy hand of the early hypopituitarism,* called the *"type en petit,"* and the *short, stocky, spade hand of the acromegalic,* termed the *"type en large."* The only differences between this type of hand and that of postadolescent hyperpituitarism of the anterior lobe, as shown in the acromegaly, are the *length* of the fingers, the *character* of the *finger ends,* and the *hair covering of the wrist and fingers.* While the fingers are large and long in these cases, they are perfectly formed, and *do not* tend to *clubbing at their ends.* The white crescents of the nails are usually prominent. Roentgenogram of the individual fingers shows *slight* tufting and increased tuberositeal growth, yet not the marked *mushrooming* or *exostosis* of the terminal phalangeal tuberosities present in the acromegalic hand. The wrist bones are overdeveloped, producing a wrist that is just as wide as that of acromegaly; but it is less conspicuous than in acromegaly, on account of the length and absence of clubbing of the fingers. The feet in a general way correspond to the hands. The toes are large, thick, and have a tendency to be flattened and widened at the tip. The arch is usually wide, and yet high. The *pelvis* in these cases *is wide and well formed;* yet, on account of the height of the individual, the absence of obesity, and the vertical position of the femur, *it gives the impression of being narrow.*

The *genital system,* as is shown in this case, is overdeveloped. The testicles are large, the penis, well developed, and there is increased local pigmentation of this organ and the scrotum. In the normal giant there is usually an absence of hypersexuality, and in the so-called eunuchoid giant there may even be a hypofunction of the gonads, with absence of secondary sexual characteristics. It is well recognized that even in the pathological giants the excessive libido present in the early stage of this dystrophy is only temporary, changing in two or three years to the exact opposite state of loss of libido and impotence. There was no marked change in the dermal system in this eunuchoid case. The absence of hair over the body is particularly noticeable, from the description (examination) and the photographs. This is one of the differential points between the eunuchoid giant and the acromegalic or pathological giant, in which the hair distribution is usually excessive, on both the torso and the extremities. The hair distribution on the face in this case was even decreased. The eyebrows did not meet above the bridge of the nose. The beard was not unusually heavy, and at the age of twenty there was no evidence of a mustache.

Physical examination demonstrated a slight enlargement of the thyroid gland, which might help to bear out the theory of Falta that all these cases of gigantism are polyglandular hypersecretions, and not due to overactivity of the anterior lobe of the pituitary gland alone. The pulse, temperature, and laboratory tests were within the normal. There was no evidence of involvement of the posterior lobe in this case. The history was absolutely negative for hormonic signs or symptoms such as polyuria, polyphagia, polydipsia, obesity, or signs of other systems, such as the gastro-intestinal, to indicate that at any time during the life of this individual there had been an anomalous secretion of the posterior lobe of the hypophysis. The absence of intracranial pressure symptoms, and the normal-sized sella turcica, demonstrate that this case, up to the time of observation, was not associated with pituitary neoplasm.

Differential Diagnosis.—On account of the height and stature of this case, *true eunuchoidism* must be differentiated. Both of these dystrophies have a *longer lower measurement than upper,* and the *span measurement is greater than the height.* The important difference between these two diseases is the development and function of the genitals. In the eunuchoid giants the genitalia are usually well developed and functionate at least as well as those of the normal individual; whereas in true eunuchoidism, in the male, they are objectively small and underdeveloped, and there is complete absence of all sexuality. Secondary sex characters are more or less absent in both of these diseases, but more completely so in eunuchoidism than in the eunuchoid giant. Both cases may have complete absence of hair distribution and a body configuration much similar to that of the opposite sex. The eunuchoid giant, however, usually has a well-developed, deep-toned voice, which is not present in true eunuchoidism. There are minor differences with regard to the nervous organization and localized cranial symptoms. The eunuchoid giant is more likely to have an instable, excitable, emotional nervous makeup, in the majority of cases fairly well controlled. On the other hand, in the eunuchoid individual, the nervous disturbances incline to the depressive, torpid, melancholic states. Among the intracranial disturbances, the eunuchoid giant is frequently afflicted with repeated headaches, which are of the migrainous variety, associated with eye and gastric disturbances, or the peculiar "migraine ophthalmic" symptoms, without headache or abdominal disturbances, while the true eunuchoid individual has comparatively few cranial or ocular symptoms. A small percentage of eunuchoid giants have definite pressure effects upon the uncinate gyrus, producing attacks of epilepsy and subjective gustatory or olfactory symptoms, which are never present in true eunuchoidism.

Other points of differential diagnosis are the consideration of the participation of the *individual lobes* of the pituitary gland, and the diagnosis of the *activity* of the lobes affected. Hyposecretion of the anterior lobe can be excluded absolutely by the presence of overgrowth of the entire osseous system, and at least normal development of the genitalia. Reference to Section 1, in which are contrasted the hormonic signs of hypo- and hypersecretion of the anterior lobe, will demonstrate that *inactivity* of this lobe presents exactly the opposite hormonic signs referable to both these systems, to those found present in this case. There is absolutely no evidence in this case of secretory disturbance or pathological changes in the posterior lobe. The small sella turcica and the negative intracranial symptoms prove that there is no enlargement of the hypophysis. In order to emphasize the differentiation of the *overactivity* of the *anterior* lobe, occurring *before* and *after* maturity, the hormonic signs due to hyperactivity of this lobe present in the pre- and postadolescent varieties are contrasted in table 6.

TABLE 6. ANTERIOR LOBE HYPERPITUITARISM

	Pre-adolescent	*Post*-adolescent
A. Osseous System	A. *Long bone* overgrowth.	A. *Acral, short, and flat bones* thick-dense and blunted.
1. *Height*	1. Very *tall.*	1. *Short, stocky.*
2. *Proportions.*	2. Normal, in comparison with height.	2. Abnormal. Head, hands, and feet large compared with body.
3. *Station.*	3. *Erect.*	3. *Stooped.* Round shoulders.
4. *Head.*	4. Classical features and shape.	4. *Hexagonal.*
5. *Hands.*	5. "*Type en longe.*"	5. "*Type en large.*" *Spade hand.*
(*a*) Fingers.	(*a*) Long, wide, with *rounded* tips.	(*a*) Short, wide, with *clubbed* tips.
(*b*) Nails,	(*b*) *Large, crescents showing.*	(*b*) *Small.* White *crescents buried beneath overgrowth of dermal tissue.*
(*c*) Phalanges (*x*-ray).	(*c*) Tuberosities *slightly* tufted.	(*c*) Tuberosities *mushroomed* and *exostotic.*
	Bones long, not overdense.	Bones short, very dense and thick.
6. *Feet.*	6. *Proportionately* large.	6. *Unproportionately* large.
(*a*) Toes.	(*a*) Long, slender.	(*a*) Short, with clubbed ends.
B. Musculature.	B. *Proportionate* development.	B. *Unusual* overdevelopment.
C. Neck.	C. *Long.*	C. *Short.*
D. Hair Distribution.	D. Increased on *torso,* especially chest.	D. Marked increase on *distal extremities.*
E. Genitalia.	E. Enlarged *in proportion to height.*	E. *Unusual development, disproportionately* to height.
1. Gonad Function.	(*a*) Early *loss.*	(*a*) *Hypersexuality maintained* for years.
F. Mentality.	F. Normal or *decreased.* Early depression.	F. *Heightened* development. Loquaciousness. Instability.

It will be noted, in comparing the hormonic signs due to overfunction of the anterior lobe occurring before adolescence, with those occurring after adolescence, that the chief differences in the osseous system are those referable to the long bones as compared with those of the short and flat bones. In the pre-adolescent variety the long bones are almost exclusively involved. This has a tendency to produce a *eunuchoid type of individual,* with a marked *increase of the lower length over the upper length.* In the postadolescent type this hormone of growth reactivates the osseous nuclei in the short and flat bones, producing a decided overgrowth in such bones as the flat bones of the skull, the maxillæ, the vertebra, and the carpal and metacarpal bones. The overgrowth of these bones produces exactly the opposite proportions in the length; that is, the *upper length is* very *much longer than* the *lower length.* The torso seems to be very much elongated, whereas the extremities, particularly the lower, are decidedly shortened. The overgrowth of the carpal and tarsal bones produces a very wide wrist and ankle. This, taken with the undergrowth of the long bones of the hand, produces a short, stubby hand, in which the tuberositeal prominences of the terminal phalanges are decidedly mushroomed or exostotic. The overgrowth of the musculature, particularly in the postadolescent type, contrasts very strongly with the overdevelopment of the adiposity in the exact opposite secretion of the posterior lobe of this gland. The hair distribution in the pre-adolescent seems to be confined to a large extent to the torso, whereas in the postadolescent the extremities and lower abdomen are more decidedly involved. The genital function in the pre-adolescent is usually one which is very much inclined to be decreased. If it is hyperactive at all, this overactivity is usually of a limited time of a few years. On the contrary, the hypersexuality of the postadolescent or typical acromegalic is frequently continuous during the entire life, or at least long into the postadolescent age of the individual. There is also a striking difference in the mentality of these two individuals. In the pre-adolescent the hypermentality has the same tendency as the sexuality, to be early exhausted and change into one of depression and deficiency. In contrast with this is the marked hypermentality and loquaciousness of the postadolescent hyperactivity of this lobe of the gland, persisting during late adult age.

Complications, Sequelæ, and Associated Diseases.—With the exception of a possible slight hyperthyroidism, there were no complications, sequelæ, or associated diseases. Additional diagnostic evidence indicating a hyperthyroidism was shown by physical examination of the heart. The whole precordia presented a marked systolic impulse, ranging from the third to the fifth interspace, within the nipple line. Over the pulmonic area there was a loud systolic murmur, which disappeared entirely on deep inspiration, and there was a positive "tittat" phenomenon over the gladiolus. *The above combination of an enlarged thyroid and cardiac physical signs has been so constantly found in hyperthyroidism that the writers have interpreted this cardiac symptom-complex as one of "thyroid heart."* The explanation of the systolic murmur over the pulmonic area, being projected upward toward the scapuloclavicular joint of the left shoulder, has been accounted for by probable enlarged thymus changes, associated with thyroidism. The fact that this murmur, as well as the peculiar "tit-tat" phenomenon over the gladiolus, closely mimicking a short, pericardial rub, disappears entirely during the latter phases of inspiration, has led them to believe that the murmur is due to a partial compression of the left pulmonary artery. This artery, on leaving the right ventricle, courses upward and forward, in apposition with the posterior surface of the thymus and the sternum. Any enlargement of the thymus would naturally produce a compression murmur at this point. The further fact that the *murmur does entirely disappear during deep inspiration, when the anterior portion of the chest is raised* upward and forward, *away from the pulmonary artery,* is considered additional argument for this explanation of the production of the systolic murmur. This murmur is ordinarily called a hemic or functional murmur, for which various causes have been assigned, nearly all of which, however, are non-mechanical in origin, and have no relation to thyroidism or to possible thymus involvement. If this sign does have any relation to the thymus, it might further implicate, in this individual case, changes in this endocrinous gland. This would be further proof bearing upon Falta and Meyers' contention that these cases are not uniglandular in origin, but merely the objective evidence of a polyglandular hypersecretion, without any one gland being the initial or predominating etiologic factor.

Clinical Varieties.—There have been various etiological and clinical classifications of gigantism. The first valuable description of this dystrophy was made by Langer, who distinguished between the *normal* and the *pathological* giants. Under the pathological giants, he first called attention to certain osseous changes, such as the relatively small cranium, associated with an enlarged sella turcica, enlargement of the facial bones and sinuses and increased development of the muscle insertions, and abnormalities of the pelvic girdle—changes which were later described as acromegaly. He also pointed out the localized changes in the soft parts, such as enlargement of the tongue and lips. Sternberg first described the combination of acromegaly and gigantism. He states that 40 per cent. of all the giants are acromegalics, and 20 per cent. of all the acromegalics, giants. Massalongo describes acromegalia as late gigantism. Brissaud and Meige were the first to attribute both of these conditions to function of the pituitary gland, stating that they differed merely in change of this function, occurring before and after ossification of the epiphyseal junctures. They contended that only the acromegalic giants should be termed giants proper, and that gigantism should also be regarded as a disease. This contention was contradicted by Pierre Marie, Launois, and Roy. The researches and monographs of these authors show that the greater part of the giants thus far observed have been acromegalic, or have later become acromegalics. Biedl agrees with the latter opinion, and has classified gigantism among the hypophyseal diseases. The difficulty in definition arises in fixing the arbitrary limits of gigantism, both as to size limits of normal and gigantic individuals, and as to the etiology of gigantism. Bollinger proposes the height of 205 cm. as being the dividing line between the normal individual and the giant. French authors, as stated above, contend that only those giants bearing acromegalic features should be considered true giants. Falta adheres to Langer's classification of dividing these dyscrasias into the normal and the pathological giants. He has added to this type a *eunuchoid gigantism,* which Launois and Roy have termed *infantile gigantism.* Falta does not classify gigantism among the pituitary diseases. He believes that the enormously increased tendency to growth of the entire body present in this dystrophy signifies "a rendering potent of the *entire ductless glandular system,* that is mostly followed by rapid exhaustion, in which some glands, as, for example, the sexual glands, even at the beginning of the disease, show signs of loss of function and maldevelopment." He says that the problem of whether there is justification regarding the potentizing of the ductless glandular system as the cause of increased tendency to growth, or whether from the beginning there was an abnormal tendency of the entire organism, including the ductless glands, to overgrowth, is a question. He believes that gigantism is a *polyglandular hypersecretion,* and classifies it as the *opposite syndrome* to *multiple ductless glandular sclerosis,* the clinical manifestation of deficiency of a number of glands, particularly the thyroid, the gonads, the hypophysis, and the suprarenals. This polyglandular sclerosis produces a mixed picture of hypothyreosis, eunuchoidism, and hypophyseal insufficiency, combined with a syndrome similar to Addison's disease. Especially brought into prominence by this multiple glandular sclerosis is a progressive, uncontrollable, high-grade cachexia.

The writers, following the earlier grouping of Brissaud, Meige, Marie, Launois, Roy, and Biedl, have classified gigantism among the preadolescent hypophyseal dystrophies. They believe that it is an expression of a hypersecretion of the anterior lobe occurring during the preadolescent age, or at least previous to the completion of epiphyseal ossification. This has been proved by autopsy (Cushing, Launois, and Roy). That there are other endocrinous glands secondarily involved is as true in this condition as in the hypopituitarisms, thyroidisms, or any other dystrophy having change in the function of a single ductless gland. They are convinced that, for the advancement of the knowledge of these diseases, to determine, if possible, the individual gland whose original disturbance of function was the cause of the later polyglandular imbalance, is the prime essential in each case. The proper etiological correlation of the internal secretions of these cases is necessary in order to clear up the present chaos existing in the literature. For this reason, their clinical classification is as follows: Gigantism will be anatomicophysiologically classed as an *anterior lobe pre-adolescent hyperpituitarism.* The clinical subdivisions of gigantism will be (A) *normal* and (B) *pathological* giants, as grouped by Langer. The pathological giants will be subdivided into the clinical groups designed by Falta, of (1) *eunuchoid* and (2) *acromegalic* giants. Considering the height of the average normal individual as being 5 feet 9 inches (175 cm.), a height of over 6 feet 6 inches (198 cm.), in order to arbitrarily fix the stature height of gigantism, is considered applicable to this type of individual. The general *proportions* and *pathological hormonic signs* will be the basis of differentiation between *normal* and *pathological* gigantism. For instance, the normal giant is perfectly proportioned, without signs of either eunuchoidism or acromegaly. The pathological giants are characterized by disproportions, being gigantic individuals with abnormality of makeup indicative of either eunuchoidism or acromegaly. A normal giant is then defined as a *well-proportioned* individual above 6 feet 6 inches in height, who does not have any local objective changes in the sella turcica or constitutional hormonic signs of disturbed pituitary function, other than that of *well-proportioned overdevelopment* of *all* the bones and *other* structures. Under the pathological types, *eunuchoid gigantism* is that clinical type of this height, without genital hypoplasia or hypofunction, having an *increase of the upper over the lower measurement,* and of the *span over the height.* The *acromegalic giants* are those having the characteristic general overdevelopment of the body, of a pre-adolescent hypersecretion of the anterior lobe of the pituitary, *to which have been added the specific changes present in the overgrowth* of the *short* and the *flat bones,* particularly the *head, face, hands,* and *feet.*

Treatment.—PROPHYLACTIC.—The relation of acute infections, traumata, and the physiological epochs of puberty and pregnancy, to the dysfunction of the pituitary gland, has not been sufficiently appreciated. While this has not been as notably exemplified in the *hyper*secretions as in the *hypo*secretions, it undoubtedly is an important fact to bear in mind. With regard to instituting early prophylactic treatment, the incidence of secretory disturbances of the pituitary following especially the above diseases and changes, has a definite bearing. The well-known hormonic signs and symptoms of pituitarism, such as changes in osseous growth, adiposity, polyuria, disturbances of metabolism, blood-pressure, etc., following the above etiological factors, should be more carefully noted and treated as early signs of pituitarism.

ACTIVE.—The treatment in eunuchoid gigantism, of which this case is considered an example, should consist merely of careful, prolonged **observation.** So long as there is no definite focal disturbance of the pituitary gland, or evidence in the rest of the body of constitutional signs or symptoms indicating pathological changes due to an abnormal amount of secretion from the anterior lobe, treatment is unnecessary. It should be borne in mind, however, that these cases are subject to two changes which might at any time require relief. One is the possibility of *strumous growth in the pituitary gland,* and the other is the *change of activity of the anterior, or both lobes of the pituitary gland,* to one which might produce serious hormonic constitutional manifestations. While there is no prophylaxis that can be given to prevent such changes, the patient should be advised to undergo regular observations, in order to make their early discovery possible. It is well known that the course of these hypersecretions of the anterior lobe is extremely variable and differs decidedly in the individual cases, as will be shown in discussing the progress of the disease under the subject of prognosis. Those cases that have a continuous well-balanced hypersecretion, without local or systemic symptoms, probably require no special treatment. Even in the cases with definite oversecretion, the writers have found indications for exposing these patients to **x-ray and radium**, in order possibly to prevent the later changes occurring in the great majority of the normal giants. While there are undoubtedly a considerable number of these individuals who apparently are free from any disturbances, except their overgrowth, if these cases are carefully analyzed, it will be seen that they are really suffering from minor internal secretory imbalance, evidenced by nervous instability, decreased muscle capacity, and *minor hyperactivities of other ductless glands,* particularly the thyroid, gonads, and adrenals. It may be possible in cases of secondary hyposecretion, by inhibiting the function of the anterior lobe of the pituitary, not only to avoid future serious changes in this gland, such as complete inactivity and struma, but also to maintain the normal secretory function of other endocrinous glands, particularly the thyroid, the gonads, and the adrenals. It would be exceedingly interesting to observe the effect of this inhibitory treatment of the pituitary gland, as related to that of hyperthyroidism. The interrelation of the secretory disturbances of these endocrinous glands is undoubtedly a fertile field for investigation, and this can be carried out by means of the clinical study of the effect of modifying the secretion of one gland upon the functions of other endocrine organs. Those cases having recrudescences of hypopituitarism require at such times **substitution of anterior lobe secretion.** Those cases which finally develop into decided continuous and progressive hyposecretions require the ordinary treatment of hypo-activity of this lobe, outlined in the previous chapter. Those which finally change into neoplasm of the pituitary require the ordinary **surgical** and **postoperative preventive treatment** for recurrences.

Prognosis.—While the normal giant is ordinarily considered an unusually good physical specimen, with an extraordinary muscular development, the contrary is true. It has been shown that these individuals do not have a physical capacity above the average, that, in fact, at an early age they have extreme muscular weakness. Their nervous poise and stability is undoubtedly below the normal. This is probably due to complications of other secretory disturbances, particularly those of the thyroid and the adrenals. It is well known that individuals affected with pathological gigantism have a short duration of life. Hutchinson's analysis of 8 cases showed that the average duration of life had been only twenty-one years. The giant Chang died at the age of fifty-one, and the giant Palozzi, reported by Levi and Franchini, reached the unusual age of sixty-six. This class of giants (pathological), however, have clinical syndromes of various local or constitutional manifestations, which occur early in the course of their gigantism. The normal and the eunuchoid giants are comparatively free from these hormonic disturbances. The neoplastic changes in the hypophysis itself are usually postponed until late in these two varieties. Even these cases, however, are subject to one of the following courses: (1) They may remain in a mild, latent hyperactive stage of the anterior lobe of the pituitary for a considerable number of years, or even throughout life. (2) A certain percentage of these cases have recrudescences of hypo-activity, occurring for longer or shorter periods. (3) Some of the cases ultimately change into a complete hypo-activity, in which the posterior lobe, as well as the anterior, finally takes part. These cases finally drift into a complete bilobar hypopituitarism. (4) A certain percentage of them change into the pathological giants, having either local changes in the pituitary gland or distressing hormonic signs, either of eunuchoidism or acromegaly. One can well understand how the different courses in the individual cases modify the prognosis. Those changing into a hypopituitarism, and those developing hypophyseal tumor, are the most unfavorable. The secondary hypopituitarism resulting from a primary hyperactivity of the anterior lobe is not nearly so favorable, on account of its more refractive reaction to treatment, as the primary hypopituitarism involving either one or both lobes of this gland. Hyperpituitarism, as a division, is much less favorable prognostically than are the hypopituitarisms. This is due to the difficulty in inhibiting the functional activities of this gland either by surgery or radio- or roentgenotherapy. The writers have found that this group of cases are certainly not medical, in the sense that they react at all to glandular or medical treatment. A certain percentage of the hypopituitarisms which have not been preceded by hyperactivity of the gland or are not due to neoplasm of the hypophysis, on the other hand, do react to the proper glandular treatment.

Pathology.—The pathology of eunuchoid gigantism not producing pituitary or neighborhood signs or constitutional hormonic manifestations, cannot be given. One would suspect that there is a simple hyperplasia of the anterior lobe which has not been advanced to the so-called "adenomatous cluster" described by Lewis and Benda in the pathological cases. That the lesion is located in the anterior lobe is now accepted by nearly all authors. There is complete absence of changes of function in the infundibulum or the posterior lobe of the hypophysis. Changes in other portions of the body due to the hypersecretion of this lobe are limited almost entirely to the osseous and genital systems, with secondary changes in other endocrinous glands. In the pre-adolescent variety, as described in this section, the osseous changes are most decided. These consist in overgrowth of all the bones of the body. All the long bones have unusual length measurements. The flat bones are increased in size in all dimensions, and the short bones undergo the same changes of overgrowth. Particularly characteristic of the overactivity in the acromegalic giant is the overgrowth of the tuberosities and the exostoses at the muscle insertions of all the bones. This is most easily demonstrated in the terminal phalanges of the hand by roentgenographic pictures. The slight tufting, but never exostoses, of the small tuberosities of the terminal phalanges of the fingers and thumb, is among the most valuable differential signs of this disease, in the normal and eunuchoid giants. Retention of the epiphyseal lines late in life demonstrates the late closure of the ossifying nuclei of the bones in eunuchoid gigantism. It is not only the bones of the long shafts and the peaked bones that are involved in this overgrowth. Especially in the acromegalic giants, the flat bones of the head and the pelvis undergo the same changes in size, as can be demonstrated by the actual increase in the size of the head and the measurements of the pelvis. The large sinuses, the prolongation of the nasal bone, and the size of the mandible, as well as of the maxilla, show the effect of the stimulating hormone from the anterior lobe. This corresponding overgrowth of all the bones in the *normal giant* allows the general proportions of the individual to be undisturbed, with the exception of some slight changes in the face, such as protrusion of the upper maxilla, the posterior position of the ear, etc. It must be remembered that these bony changes of overgrowth remain permanent throughout the course of the disease, even in those cases in which the function of the anterior lobe changes to a complete inactivity. The same is true of the bony changes in postadolescent overactivity of the anterior lobe, as seen in the acromegalic. The osseous changes in the peaked bones of the hands and face are constant fixtures throughout the entire course of the case, and consequently do not in themselves indicate a hyperactivity of the anterior lobe at any one time of observation. On the contrary, these changes, as well as those in the pre-adolescent variety, merely indicate that there was at some time previous to the observation a pronounced hypersecretion of this lobe, either before or after epiphyseal ossification. Histological change in the gonads themselves has not demonstrated marked changes during the active stages of normal gigantism. In those cases which are later followed by hypopituitarism, the testes in the male have shown diffuse fibrosis, with an almost complete absence of the cells of Sertoli. Brissaud and Meige have described a combination of gigantism and infantilism (eunuchoid gigantism). They refer, however, in this description, more to the absence of secondary sexual characters, which gives a pre-adolescent aspect to their "grands enfants viellotts." The changes in other endocrinous glands, particularly the thyroid, the thymus, and the adrenals, have also shown marked hypoplasia in those late cases of gigantism which have changed to hypopituitarisms. In the state of hyperactivity of the anterior lobe, these same glands, especially the thyroid and the adrenals, are probably hyperactive. The writers are inclined to infer that this was present in the case herewith reported. The fact that the patient had a slight enlargement of the thyroid gland, a thyroid heart, a fast pulse, and a slight tremor, would substantiate the diagnosis of a co-existent slight hyperthyroidism. Hyperthyroidism has been frequently noted in other cases, many of which cannot be reported with this series. The pathology referable to the other organs and systems of the body is merely that of an hypertrophy of all the organs. Giants of all varieties have an exceedingly large brain and vessels, and usually a heart which measures and weighs more than that of the average individual. The other organs are in proportion to the general size and development of the body. In the pure anterior lobe hypersecretions there is not much change in the dermal system. In the normal and the eunuchoid giants there is absence of the hirsuties usually found in the acromegalic giant. The blood and the special sense organs in this case did not show any definite changes.

SECTION 12

ACROMEGALY

(*Anterior Lobe Hyperpituitarism, Postadolescent, Aneoplastic Type*)

Etiology.—The etiology of this disease bearing upon the late hypersecretions of the anterior lobe is much the same as that of the early dystrophies of this lobe. It is probable that pregnancy and conception have more effect in actually producing acromegaly than does trauma or infectious disease. Erdheim and Stumme have demonstrated marked hyperplasia and enlargement of the anterior lobe of this gland present in pregnant women. In some of these cases this stimulation of the activity of this lobe continues after pregnancy. The milder changes, consisting of blunting of the nose, the malar prominences, and the chin, enlargement of the hands and feet, etc., are frequently seen during pregnancy. In the majority of these cases these disappear entirely after delivery. In some, however, they not only remain, but become aggravated, developing into typical pathological acromegaly. Infectious diseases, such as typhoid, prolonged sepsis, etc., undoubtedly have the same relation to these hypersecretions, but to a lesser degree than they have to hyposecretions. The only infectious factor that was present in this case was frequent attacks of mild rheumatism. These occurred, however, after the onset of the condition, and there is some question whether the so-called inflammatory enlargements of the extremities were not merely signs of the ordinary acromegalic involvement. There was no history in this case of lineal ductless gland ancestry, although the entire family history could not be accurately obtained.

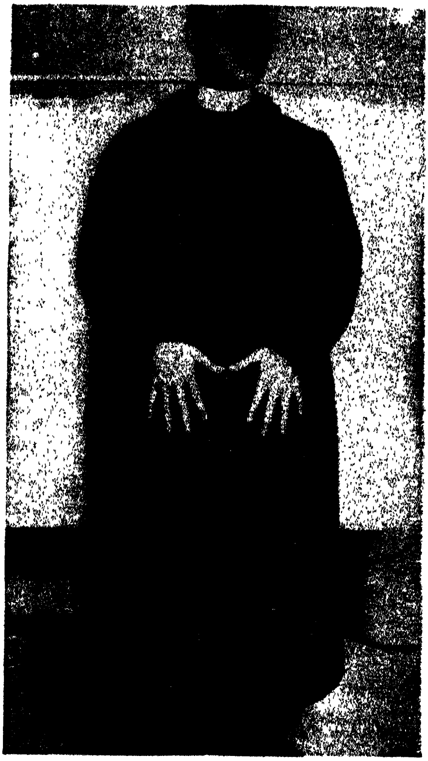
Symptomatology.—HISTORY: CASE XXV.—Rev. G. J., St. John's Hospital, General No. 258, October 29, 1917.

Present.—Chief Complaints: (1) *Marked perspiration of the hands and feet,* slight in the armpit; (2) *increased prominence of the inferior maxilla and the malar bones;* (3) *enlargement of the hands and feet, and clubbing of the fingers and toes;* (4) *shooting pains in the hands and lower extremities* from the wrists and ankles down, one-half minute in duration.

Duration.—Thirteen or fourteen years.

Course.—(*a*) *Onset:* Gradual. The patient first noticed *enlargement of the hands,* especially *clubbing of the fingers.* Associated with this, he noticed an *increased thickness and breadth of the palm,* and at times *swelling of the phalangeal joints. The skin of the hands would become very tight.* This swelling was not accompanied by any pain, but by marked stiffness. The *swelling would last for about one day, disappear* *for a short time,* and *reappear without known cause.* The patient also noticed *corresponding changes in the feet,* as to clubbing and swelling.

(*b*) *Progress.*—This gradually continued, but at no time was there any marked change. Along with the increased size in the hands and feet, the patient noticed *marked perspiration of both.* At times the hands and feet become *blanched and cold, at which time the skin is dry.* This condition lasts but a few minutes, when hands and feet become of a normal color, followed by marked perspiration. The patient notices *no abnormal perspiration in any other portion of the body, except in the armpits,* which is very much less than that of the hands and feet. The perspiration seems to extend from the ankle down, and from the wrist distally. This condition is gradually becoming worse with age. About four years ago the patient observed a *change in his face*—marked *prominence of the malar bones, nose,* and *inferior maxilla.* He has noticed no change in the distances between the teeth of the inferior maxilla. *The size of the hat is the same as before the onset.* He has noted especially that the distance from the supra-orbital ridge to the point of the chin has increased much more than the distance from the supra-orbital ridge to the vertex of the skull. At present he notices no change in mental capacity. In Germany, ten years ago, while at school, he was *suddenly seized with an attack of "numbness" in the head,* compared to the pricking of pins, located especially in the frontal region and both sides. At that time the patient's *mind was very cloudy,* the patient being *unable to concentrate or to remember.* This continued for two years, and after an extended vacation of five months, suddenly disappeared, his mind returning to normal. Since that time, the patient is of the opinion that his mind is much clearer than before, and he is able to do now with ease what previously was impossible, such as learning foreign languages, etc. For the past years there has been *some loss of hair,* and at times it can be pulled out of the scalp in large quantities. The size of the nails has increased in proportion to the remainder of the hand, but at present the nails seem rather *small in proportion to the hand.* When the hands and feet are not perspiring freely, the *nails* are like glass, *very brittle.* The patient uses care in picking up articles, in order to prevent breaking the nails. In the past eight years he has also noted an *increase of hair about the body,* especially over the anterior chest and the thighs. There has been no marked change in the growth of hair about the face or other portions of the body. The perspiration is limited to the hands below the wrists, and to the lower extremities below the ankles, and is not accompanied by an odor. *At the onset there was also hypersexual function,* in the form of nocturnal discharge, which at first occurred two or three times a week, but *at present is gradually decreasing in frequency* to once or twice every two months. *With the onset* of symptoms he also noticed *increased excitability,* and *irritability.* The patient was *very nervous,* and *worried a great deal.* For the *past two or three years,* however, his *disposition* has *entirely changed.* He is *calm and quiet,* and *not* very *easily irritated.* He is subject to *attacks of vomiting,* which are sometimes brought on by the mere mention of certain articles of food. This vomiting is not accompanied by nausea. The attacks are worse in the morning on arising, and at intervals occur as often as every morning. He has been troubled with these gastric symptoms for one and one-half years. There has been a *marked constipation* for the past year. The patient has noted no changes in other bones of the body.



CASE XXV. Fig. 1.—Note Short, Heavy Stature, with Good Muscular Development, without Obesity, Broadness of Hands, and Prominence of Jaw.

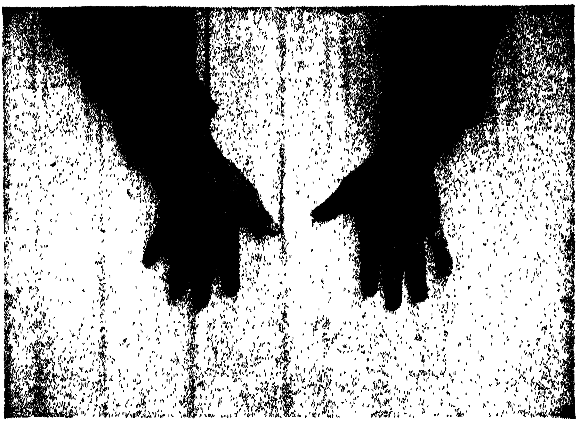
Past.—The patient has always been healthy. Several attacks of rheumatism in the past three years, when joints have become swollen and hot. No tenderness in the balls of the feet or the heels.

Personal.—Coffee moderately, alcohol moderately. Denies history of venereal disease.

Family.—Father dead, cancer of the stomach. Mother, condition unknown. Three brothers living, well. Two sisters dead, exact causes unknown. No family history otherwise of hereditary diseases.

Examination.—*Physical.*—Height, 5 feet 8½ inches (174 cm.); weight, 185 pounds. *Muscular development marked,* nutrition not decreased. Color good. No cyanosis, dyspnea, or edema. No abnormality of gait or station. *Abnormal distribution of hair* about *the upper chest, abdomen,* and *above the clavicles, at the lateral aspects of the neck. No abnormal deposition of fat. Hands and feet very moist,* considerable perspiration in axillæ. *Striking feature is the large size* of the *hands and feet. Extreme breadth of the palm, digits wide, fingertips blunt.* Feet of same character, broad at the instep, with broadening of metatarsals and phalanges. Measurement around palm (as for glove), 10 inches (25.4 cm.); measurement through instep, 10½ inches (26.6 cm.). Long bones *not* abnormally developed Distance from olecranon to styloid process, 11 inches (28 cm.); from jugulum to umbilicus, 15 inches (38 cm.); from umbilicus to symphysis, 8 inches (20 cm.); from jugulum to symphysis, 23 inches (58 cm.); from jugulum to ensiform, 9½ inches (24 cm.); from ensiform to symphysis, 13½ inches (34 cm.); from greater trochanter to external malleolus, 33 inches (84 cm.). Temperament, phlegmatic. Pulse, slow, regular, good volume and tension, no particular character, equal, symmetrical. Temperature constantly subnormal. (*Hands perspire very profusely during examination.*)

Regional.—Head: Large, well formed, symmetrical. *Marked prominence of the jaw.* Nose *slightly blunt,* but not markedly so. The patient remarks that the portion of the face from the malar process to the tip of the chin has changed decidedly in shape and fullness in the past five or six years, and the nose has become more blunt in appearance. (Changes in the hands and feet have been markedly noticed.) Hair rather thin, not particularly dry, of good texture. No change in pigment of the hair, some frontal, vertex alopecia. No localized compression tenderness over sinuses, muscle attachments, or nerve exits. *Face:* Rotund, with some tendency to a *hexagonal type.* Temporal vessels not visible. *Ears:* Air conduction very slightly decreased bilaterally. Bone conduction normal. Rinne's test negative. External ears well colored, no tophi. *Eyes:* Eyebrows of normal thickness, lashes also normal. Palpebral slits narrow, *eyes rather deep-set.* Very slight tremor of the closed lids. Eye-muscles intact, no thyroid signs. Pupils equal, regular in contour, react promptly to light and to accommodation. Convergence and divergence without nystagmus. Scleræ free from pigment. *Nose:* Septum slightly deviated to the left. Mucous membranes normal. *Mouth:* Upper incisors short, heavy in type, *without separation.* Very slight pyorrhea of the lower teeth. Number of teeth missing. Mucous membranes of normal color, free from lesions and pigmentations. Tonsils not visible; pharynx slightly injected. *Neck:* Diffuse *thyroid fullness,* without distinct enlargement. Slight diffuse pulsation in this region. Pulsation visible in the jugulum and over the carotids; veins not visibly pulsating. Lymph-glands not palpable. *Chest:* Well covered, broad. Abnormal distribution of hair about the upper and lower portions. Vertebral column straight. Several pigmented spots about the back. Percussion note of normal resonance; tactile fremitus equal, symmetrical, not increased. Occasional fine râle heard in the lower left base, no rubs or other adventitious sounds. No increased transmission of voice, whispered, or breath sounds. *Heart:* Apex-beat not distinctly visible. Very faint impulse in the fourth interspace, two fingerbreadths within the nipple line. Heart borders,—apex-beat, fourth rib, left sternal border. No diastolic shock, thrill, or bruit palpable. Sounds, apex,—slow, pure, regular. *Slight systolic murmur in the pulmonic area on complete expiration, which disappears on complete inspiration.* Aortic area normal, tricuspid the same. No abnormal signs over the large vessels of the chest or neck. *Abdomen:* Broad, short, with wide intercostal angle. Few pigmented spots. Abnormal distribution of hair as referred to. No visible pulsations. No tumefactions, rigidity, or tenderness. Tympany throughout. *Liver, kidneys, spleen, stomach, colon* and *rectal examination* normal. *Genitalia:* Remains of an old epididymitis on the left side, tenderness still present, no acute inflammation or enlargement at the present time. *Penis large, testicles well developed. Extremities:* Feet and hands as described, broad in makeup. No padding about the ankles. Perspiration of the hands and feet profuse. No edemas or varicosities. *Reflexes:* Normal.



CASE XXV. FIG. 3.—NORMAL SELLA TURCICA, SHOWING NO EXCAVATION OR EROSION. FINGERS, WITH BLUNTING.

LABORATORY FINDINGS.—*Urine.*—Single specimen, color straw, reaction acid. Leukocytes, 1 to 2 to high power field. Dextrose, albumin, casts, and erythrocytes negative.

Blood:

Wassermann	negative
Erythrocytes	4,760,000
Leukocytes	14,200
Hemoglobin	98 per cent.
Stained smear	normal

SPECIAL EXAMINATIONS.—*Roentgenogram of Head* (Transverse View).—No abnormality of the sella turcica. Anterior and posterior clinoid processes not displaced or eroded. No excavation of the floor of the sella.

Roentgenogram of Hand.—Characteristic broadening of the metacarpals and phalanges. Decided characteristic lipping of the unguinal phalanges.

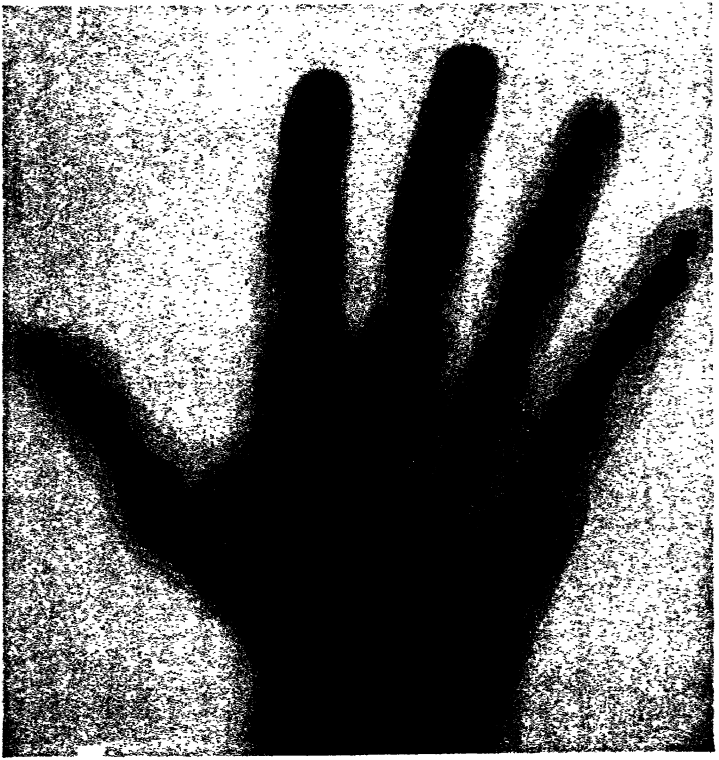
CASE XXV. FIG. 3.—NORMAL SELLA TURCICA, SHOWING NO EXCAVATION OR EROSION.

COURSE IN HOSPITAL.—(11-12-17.) Since admittance into the hospital, the patient has been complaining of swelling of the feet. His last shoes, bought during the summer, were size 8½, but since coming to the hospital he has bought three pairs, the last being size 10.

(11-14-17.) **Anterior lobe extract of pituitary,** minims xvi (1 c.c.), injected intramuscularly. Ten or fifteen minutes following the injection, the hands and feet were free from perspiration, and remained so until the following morning, when beads of perspiration returned as before.

(11-15-17.) **Pitrenalin,** minims xvi (1 c.c.), injected as above, with slight results, of lesser duration.

REËNTRANCE HISTORY (March 18, 1918).—*Chief Complaints:* (1) *Marked perspiration of the hands and feet;* (2) *swelling of the hands and feet, causing stiffness;* (3) shortness of breath; (4) *tympanites,*



CASE XXV. FIG. 4A.—NOTE BROADENING AND SHORTENING OF METACARPALS AND PHALANGES, WITH DEFINITE MUSHROOMING OF UNGUINAL PHALANGES.

CASE XXV. FIG. 4B.—COMPARATIVE STUDY OF HAND OF BILOBAR HYPOPITUITARISM.

Note increased length and decreased width of metacarpals and phalanges, and pointing of terminal phalanges, in contrast to tufting of opposite figure.

continuous, associated with *belching, vomiting,* but *no nausea;* (5) *oliguria;* (6) *constipation.*

Course.—Since the patient's dismissal from the hospital in November, 1917, the general course has been about the same. The patient still complains of marked perspiration of the hands and feet, accompanied by swelling and stiffness, producing inability to close the hand. While at home he has taken *anterior lobe pituitary extract, extract of pineal body,* and *antipituitary extract.* These have had little effect upon the local condition. However, hypodermic injections of *anterior pituitary extract tend to dry up the perspiration immediately, being effective for from twelve to eighteen hours.* For the past two weeks the patient has noticed *shortness of breath* and a feeling of *pressure, weight,* and *suffocation in the chest,* especially brought about by exertion, not influenced by position. He also has developed a feeling of *distention* and *tympanites* of the abdomen, with very *occasional pain, accompanied by belching,* which offers some relief. The bowels have been *somewhat constipated,* but bowel movement does not relieve the distention. On several occasions there has been a feeling of weight and *distress in the abdomen,* which was *relieved by vomiting, unaccompanied by nausea.* The patient noticed that he vomited food which had been taken eight or ten hours previous. The *amount of urine* passed is *markedly decreased,* being apparently not more than one and one-half pints daily. He has noticed no further change in the size of the hands and feet, and has not been compelled to buy a new pair of shoes since leaving the hospital. He has observed that the hands perspire more freely when hanging down. The trousers have become tight about the waist, probably due to the distention produced by gas.

REËXAMINATION (LABORATORY FINDINGS).—(1) *Urine.*—(*a*) Single specimen, color straw, specific gravity 1.025, reaction alkaline. Trace of albumin. Dextrose, erythrocytes, leukocytes, and casts negative. Triple phosphate crystals present.

(*b*) Twenty-four-hour specimen, 1,000 c.c., color straw, specific gravity 1.025, reaction acid. Trace of albumin. Dextrose, erythrocytes, leukocytes, and casts negative.

(2) *Blood-sugar* (August 24, 1918): 0.080.

SUBSEQUENT TREATMENT:

March 19, 1918.

(1) **Thyroid extract,** grain ss (.03 gram) t.i.d.

(2) **Anterior lobe pituitary extract,** minims xvi (1 c.c.). 'H' daily.

April 5, 1918.

(1) **Anterior lobe pituitary extract,** minims xvi (1 c.c.) } 'H' daily.
(2) **Posterior lobe pituitary extract,** minims iv (0.24 c.c.) }

April 24, 1918.

(1) **Pituitary extract,** minims vii (0.42 c.c.), 'H' given for distention and marked tympanites of the abdomen. Ten to fifteen minutes after the injection of this amount of pituitrin (S) the patient began to pass a considerable amount of flatus and had a bowel evacuation; and

within two hours afterward the abdominal distention and discomfort were relieved entirely.

After leaving the hospital the patient had recrudescences of swelling and enlargement of the face, hands, and feet, with marked localized perspiration. These were decidedly affected by the injection of **extract of anterior lobe pituitary gland,** and after a series of six or eight injections would frequently be absent for a number of weeks at a time. No other symptoms of abdominal ballooning occurred during the course of three months following discharge from the hospital.

Note: Course Since Last Observation. September 30, 1918.—The patient states that his hands swell rather decidedly at times, more noticeably during rainy weather. Yellow chloasmic pigmentation comes and goes. The face and feet do not change perceptibly in size. Perspiration is very much less, causing the parts affected to become moist, but not drenched, as at the previous examination. During the last five days he has had frequent attacks of vomiting, but without extreme distention of the abdomen, as present during his stay in the hospital. He has had very occasional mild headaches, without ocular disturbances. He has gained 17 pounds in weight since leaving the hospital. The patient has taken only a few injections of **anterior lobe pituitary gland** since the last observation, but has taken anterior lobe pituitary gland by mouth, grains ii ss (0.16 gram) after meals.

Reëxamination.—No marked gross changes, except ecchymosis of the right inguinal region, due to injury received a few days ago. *Measurements:* From vertex to symphysis, 35½ inches (90 cm.); from symphysis to soles of feet, 33½ inches (85 cm.); span, 72 inches (183 cm.); circumference of head, frontal region, 22 inches (56 cm.); at upper maxilla, 20½ inches (52 cm.); at tip of chin, 21 inches (53 cm.); above tip of chin, 20½ inches (52 cm.); circumference of hand (both right and left), 9¼ inches (23 cm.). Heart and lungs negative.

Diagnosis.—The diagnosis of this case is a *postadolescent hypersecretion of the anterior lobe, free from pituitary tumor.* The history states that the patient was free from all signs of acromegaly *previous* to the age of twenty-four, thirteen years before the first observation. At that time he first noticed *clubbing* of the *fingers,* especially thickening and broadening of the ends of the phalanges, associated with a marked *increase* in the *breadth of the palm,* and at times *swelling* of the *soft tissues* of the entire hand. This swelling was *unaccompanied* by any pain, but produced a marked *tightness* and *stiffness,* sufficient to disturb the function of the fingers. It was only *temporary,* lasting for a day, and would *disappear almost entirely.* At this time he also noticed similar changes in the feet. This intermittent enlargement of the feet and hands continued, and has been persistently accompanied by *localized sweating of these parts.* This perspiration has been so severe as to require almost constant attention during the day, producing large, localized water-soaked areas on the bedclothing at night. There were no other changes in the short or flat bones for eight years, or until four years previous to the first observation, at which time the patient began to notice a *decided change in the facial features.* This consisted of marked *prominence* and *rounding* of the *malar bones,* the *nose,* and the *chin.* The patient noticed especially that the *distance from the supra-orbital ridge to the point of the chin* had *increased* much more than that from the *supra-orbital ridge to the vertex of the skull.* Marked *stimulation* of the *sexual sense* was present from the onset of the disease, *for a number of years. Excitation, irritability,* and *apprehension* were among the *early* nervous disturbances. These were followed two years after the onset by extreme *psychic disturbances,* producing definite *loss of memory* and *lack of concentration,* sufficient to incapacitate the patient for attending college. This continued for two years, and then suddenly disappeared, his mind apparently returning to the normal. In the past two or three years the disposition has *changed to the opposite extreme of phlegmatic indifference.* During the course of the disease there was evidence of a hypothyroid secretion, as is demonstrated by the marked loss of hair and brittling of the nails. The patient has in the last few years developed *peculiar attacks of vomiting,* which seem to be stimulated through the gustatory sense. These are *not accompanied by nausea,* and have been produced even by the mention of certain articles of food. *Constipation* has been more prominent during this time. *Diffuse myalgic pains* throughout the entire body have been more or less *persistently present throughout the entire course of the disease.* These occur in the form of sharp, lightning pain, of one-half minute's duration. No medication, as drug, massage, hydrotherapy, electrotherapy, etc., has produced any change or prevented recurrence of these pains. Since observation in the hospital, a number of acute exacerbations of swelling of the hands and feet have been observed. In one of these, for a duration of two weeks, the patient's feet increased from a shoe size of 8½ to 10, and the hands increased two glove sizes. The perspiration was almost constantly present on the hands, feet, and face, with the exception of those times during which treatment seemed to have produced complete absence of this perspiration, varying in length from eight to twenty-four hours. There has been complete *absence of posterior lobe hormonic signs,* with the exception of one time during the re-admittance observation, when the patient complained of abdominal pains, accompanied by continuous tympanites, belching, nausea, vomiting, and some shortness of breath, which were considered as possibly due to posterior lobe hypersecretion. These symptoms disappeared after a few days' pituitrin (posterior lobe) treatment. At no time in the course of the disease was there polyuria, polyphagia, polydipsia, obesity, or hyperpyrexia. During the course of observation the pulse was continuously slow, and the temperature, subnormal. The carbohydrate sugar test showed the amount to be within the normal, that is, neither decreased nor increased.

The sella turcica was found to be absolutely within the normal as to size and shape. There was no evidence of intracranial pressure upon the optic, third, or fourth nerve, the uncinate gyrus (except vomiting?), or other structures of the brain near the pituitary gland.

The physical signs demonstrated *objective evidence of localized enlargement* of the *acral* or *peaked bones.* The chin, the malar prominences, the nose, the hands, and the feet were decidedly affected. The hands showed the classical *"type en large"* variety, consisting of a very broad wrist and short fingers, with clubbed ends—the so-called classical spade hand of acromegalia. Roentgenogram of the hands illustrated the typical *mushrooming* of the ends of the phalanges, with the short, wide finger bones and overdeveloped carpals and metacarpals. This roentgenogram affords positive differentiation between acromegaly and gigantism; for in gigantism, while there is slight tufting of the ends of the phalanges, the tuberosities are only slightly developed beyond the normal and do *not* have the marked exostotic growth, present in acromegaly. The feet had the same classical acromegalic markings. The toes were very short, wide, and broad-tipped. The nails in both fingers and toes were apparently small, on account of the overgrowth of the soft tissues about them, and the white crescents of the nails of both these parts were absent. There was no definite evidence of enlargement of the entire head, as is present in gigantism, demonstrated by the fact that the patient had worn the same size of hat as previous to the onset of the localized bony overgrowth. There was marked overgrowth, however, in the facial features, producing a fullness, rounding and *blunting* of the malar prominences, the nose, and the chin. This overgrowth, however, was not limited to the bony parts of these flat and pointed bones. The *soft tissues* were probably just as much hypertrophied as the bones themselves, and during the many exacerbations these tissues would be noticeably thickened and enlarged. That this enlargement was due entirely to these tissues could be demonstrated by the *rapid changes in size which would occur,* sometimes within twenty-four hours, in these parts. The sweating in this case was absolutely limited to those parts which were involved in this overgrowth, namely, the face, hands, and feet. There was no unusual perspiration above the wrists or the ankles on the extremities, and the remainder of the body was constantly free from moisture. There was no decided overgrowth of the long bones, nor evidence of late closure of the epiphyseal junctures. The height of the individual and the measurements of the separate long bones demonstrated that they were not beyond the normal. In fact, the majority of pathological acromegalics are shorter in stature than the normal individual. There are specific characters of the acromegalic stature which are in themselves very important to recognize. Besides the short stature there is a tendency in these individuals to have a slight kyphosis high in the thoracic vertebræ, producing a peculiar slouching, round shoulder. The neck is rather short and deep-set, and is projected forward, throwing the head forward and down between the high-placed shoulders. This position of the head, taken with the prognathism of the lower jaw and the oblique facial angle, produces a turtle-like station of the upper third of the body. These individuals have unusual muscular development, and it has been frequently noted that this is not due to any developmental cause, such as work or training. The writers have a considerable number of acromegalic individuals under observation, for instance, who have never taken any exercise or performed any labor which might be responsible for the unusual muscular development. This overgrowth of the *musculature* exists in the same proportion and probably has the same relation to *hypersecretion of the anterior lobe* in postadolescent pituitarism, as the *obesity* occurring in individuals after puberty, has to *hyposecretion of the posterior lobe.* This disproportionate muscular development is much more marked in the acromegalics than in the true giants, and these cases do not tend to the early exhaustion and muscular weakness which is present in the pre-adolescent type of overactivity of this lobe of the hypophysis. The overdevelopment of the musculature of the entire body, and the characteristic station of the shoulders, neck, and head described above, form the most constant general combination of postadolescent hyperpituitarism of the anterior lobe. There was comparatively meager hair distribution in this case, as compared with that found in the ordinary acromegalic; for in most of these cases there is an abundant growth of hair, particularly located on the extremities. The writers have frequently noted, however, that the hair of the torso usually is not so abundant in these postadolescent hypersecretions of the anterior lobe, as it is in the giants in whom this hypersecretion occurs before adolescence. The absence of pigment is noted here as a *negative* hormonic sign of importance. As was stated in the discussion under the clinical manifestations of hypopituitarism, pigmentation is taken as one of the hormonic signs of *decreased* or *inactive* secretion of the *anterior* lobe, and consequently would not be expected to be present with overactivity or increased function of this lobe of the hypophysis. The hypermentality, excitation, and irritability, followed by attacks of extreme psychosis, consisting of loss of concentration, memory, etc., are among the usual nervous symptoms present in disturbed function of this lobe. It is impossible to say, however, that they indicate either hyper- or hypofunction, as they are frequently found in clinical cases of both these states of activity. The *hypersexuality,* which was *later followed* by a *decrease in sexual function,* was the ordinary hormonic reaction constantly present in the gonads in these cases. They do not have the early depression of this function, which is present in all pathological giants, and, as long as the activity of the gland remains above the normal, their sexuality is in this same state.

Careful review of the entire course of this case would allow the conclusion that this was one of the *hyperactive diseases of the anterior lobe of* the pituitary *which had recrudescences of hypo-activity.* It is probable that there was more or less of a *constant fluctuation from an increased to a decreased functional activity* of the anterior lobe throughout the entire course of the disease. Added proof of this changeable state of function is given by the effect of medication. During certain intervals of the course very beneficial effects were obtained by administering anterior lobe extracts and substances in this case. The exhibition of anterior pituitary antiserum produced absolutely no beneficial effects upon the localized swelling and sweating of the affected parts.

Differential Diagnosis.—The differential diagnosis includes only those diseases of the hands and feet which produce enlargement and swelling, such as *rheumatism,* various *arthritides, Raynaud's disease* (on account of the symmetrical digital blanching), *gout,* and other *diseases causing general muscular pains,* such as neuritis, myalgias, etc., and, at one time, *gastro-intestinal disturbance,* producing nausea, vomiting, distention, constipation, etc. Nearly all the *infectious diseases* can be easily differentiated by the absence of general or localized signs of infection, such as temperature, increased pulse, localized redness, pain, tenderness, etc. *Myalgias, neuritis,* and other diseases causing diffuse muscular pains can be differentiated only by the inclusion of pituitary disease producing acromegaly, and by the knowledge that *pituitarism is frequently productive of severe muscular pains. Gastro-intestinal symptoms* can be differentiated by the absence of local diseases, and by the fact that *certain cases of pituitarism are associated with just such manifestations.* That the abdominal disturbances in this case reacted very quickly to pituitrin would indicate that they were probably due to a temporary hypersecretion of the anterior lobe, which is additional diagnostic evidence.

Complications, Sequelæ, and Associated Diseases.—In this individual case there were no complications or sequelæ. This case, as well as a considerable number of other anterior lobe diseases, has been comparatively *free* from other *intercurrent diseases* of any kind. The patient's past history shows a definite incidence of rheumatism, characterized by swollen and hot joints. With this exception, there was absolutely no history of any diseases. The writers have previously discussed the course of *immunity* from other diseases which anterior lobe pituitarisms follow. This is not true in the posterior lobe dystrophies. On the contrary, such patients seem very *susceptible* to a great many other infections and metabolic disturbances. Of the anterior lobe hypopituitarisms, the writers have reported 2 cases which had as complications a form of pituitary epilepsy. They have noted in the eunuchoid giants, or preadolescent hypersecretions of this lobe, one case of epilepsy. It is rare, however, to have these convulsive seizures as complications of the post-adolescent hyperpituitarisms of the anterior lobe, unless they are associated with definite neoplasm of the pituitary. Besides this striking immunity from diseases, these individuals have an *unusual tolerance for temperature changes,* and a very decided dynamic capacity for both physical and mental work.

Clinical Varieties.—The writers believe that there are *two* clinical types of acromegaly which deserve consideration. One is the so-called *normal,* and the other, the *pathological* acromegalic. The first named are undoubtedly *acromegalic individuals having all the classical hormonic signs of acromegaly,* including the osseous and the localized soft tissue changes, the peculiar mental development, the arrested, retarded growth of the long bones, the characteristic hair distribution, etc., *who do not have any changes in the sella turcica, intracranial pressure symp-*

toms, or other clinical manifestations which could be considered abnormal. The writers' acquaintance with a considerable number of individuals having, for instance, the facial features, the separation of the teeth, the spade hand, the acromegalic foot, the short, stunted stature, the loquacious temperament, etc., for a prolonged number of years, has demonstrated absolutely that they do *not* develop any abnormal signs or symptoms which would classify them as *pathological individuals.* These persons are endowed with a brilliant mentality, are usually rapid, keen thinkers and eloquent speakers, but are nearly always inclined to some instability and irrationality. They are the most intensive and untiring mental, as well as physical, workers. Their unusual musculature probably corresponds well to the peculiar mental development, giving them an enormous capacity, both physical and mental. They have much the same relation to pathological acromegaly that the normal giant has to the pathological giant. The former has the general well-proportioned overgrowth of gigantism, without having any of the pathological hormonic signs or decided disproportions present in the abnormal cases. The pathological acromegalics might be again divided clinically into the aneoplastic and the neoplastic types; that is, into those due to pituitary tumor and those free from such evidence. Diagnostic differences in these cases would depend upon the physical evidence of an enlarged sella turcica and intracranial pressure signs. It is true, however, that many of the acromegalics of the aneoplastic type have numerous *cranial symptoms.* The psychic disturbances mentioned above might be largely due to such causes. Frequent headaches, usually of the migraine type, eye symptoms, vertigo, etc., are not unusual complaints, particularly among the later ages of acromegaly. Epilepsy occurs almost as frequently in those cases having no evidence of pituitary enlargement as in those having hypophyseal neoplasm. In fact, it has occurred in the writers' series, in the hypopituitarisms without pituitary tumor, more frequently than in any other variety of pituitarism.

There seems to be no difference of opinion regarding the anatomico-physiological classification of these diseases. All authors place them unreservedly among the postadolescent hypersecretions of the anterior lobe. The posterior lobe has never been given credit for any of the signs or symptoms found in pure acromegaly. In fact, this has been the starting point of the lobar classification of these diseases, and the only difference of opinion has been that relative to the activity of the anterior lobe present in these cases. It is now well known that the hormonic signs found in acromegalia do not indicate at the time of observation *hyper*activity of the anterior lobe. They merely mean that there must have been an oversecretion of this lobe during *some previous time* which produced the overgrowth present in the face, hands, feet, etc. There are no retrogressive changes in the bones coexisting with this change of activity of the lobe from a hyper- to a hyposecretion. The overgrowth produced by the hyperactivity remains constant for a long time after the opposite function of the gland has occurred. This is one of the misleading hormonic signs, and without question has been the cause of a great many hypo-activities of the anterior lobe being wrongly diagnosed hyperfunctions of this lobe of the hypophysis. The function of the genitalia is more directly influenced by the changeable function of this lobe than is the osseous overgrowth. For example, the hypersexuality in the anterior lobe overactivities of both the pre- and the postadolescent ages usually changes decidedly into a hyposexuality. This occurs much earlier and more frequently in gigantism than in acromegaly, but it probably accompanies the change of function of the anterior lobe. This will account for the mixed picture of either gigantic or acromegalic overgrowth coexisting with the deficient function of the gonads, as evidenced by loss of libido, frigidity, and impotence, occurring in the later years of the courses of these cases. It is now also well known that hyperactivity of the anterior lobe is very apt to change sooner or later into a hypo-activity, or that there are transient states of hypo-activity present during the course of the hyperactivity of this lobe. These variable states of secretion of this lobe help to account for the marked variation in the hormonic signs present during the course of these diseases. The greatest importance that they bear, however, to clinical medicine, is that of defining the treatment. For it is well known that the treatment of a hypersecretion is entirely different from that of a hyposecretion. Consequently, the gross hormonic signs of hyperactivity cannot in themselves be taken as indications for treatment. The activity at the time of observation must be determined before proper treatment can be instituted.

Treatment.—PROPHYLACTIC.—The prophylactic treatment in acromegaly is much the same as that in gigantism. It consists of careful postconvalescent **observation** of those diseases known to produce hypersecretion of the anterior lobe of the hypophysis. This should be undertaken in order to facilitate early diagnosis of such pituitarism. Prophylactic treatment for preventing possible neoplasm of the gland, or encouraging an early hypopituitarism of the anterior lobe, easier to treat, is the same as the active treatment in those cases already well established.

ACTIVE TREATMENT.—The active treatment of acromegaly should consist first of treating possible etiological diseases which frequently produce this hyperfunction. Among these diseases, lues is the most common, the treatment of which has a decided effect upon its accompanying pituitarism. This treatment does not differ from the intensive treatment of luetic disease associated with any other important organ. The other treatment of the increased secretion of this lobe present in acromegaly consists of three methods: (1) *x-ray,* (2) *radium,* and (3) *surgery.* In those cases not having definite evidence of neoplasm or other serious intracranial pressure signs, such as ocular signs or epilepsy, **radium** and **x-ray treatment** is justified, at least for a considerable interval. On the other hand, in those cases which have pituitary tumor it is advisable to undertake **surgical treatment** first, and to follow this with roentgen or radium exposures. In those cases having longer or shorter intervals of hypopituitarism as a part of their course, the ordinary treatment for hypopituitarism, discussed under this chapter, would be indicated, at least during these intervals. The case reported herewith was one of those cases, and for a number of months at a time received considerable benefit from simple substitution of anterior lobe products. These were given in the form of **anterior lobe extract** and **anterior lobe substance,** as described in the chapters on treatment of anterior lobe insufficiency. Those cases having evidence of temporary intermittent posterior lobe insufficiency should be given the treatment for inactivity of this lobe. During one interval this case was also markedly benefited by **pituitrin** (posterior lobe) treatment. Doses of pituitrin given intramuscularly completely relieved the abdominal distention, nausea, vomiting, constipation, etc., the chief complaints during one of the reëntrance observations in the hospital.

Prognosis.—The prognosis in these cases depends to a considerable extent upon (1) the presence of pituitary tumor, and (2) the severity and progress of the hormonic signs. In those cases described by the writers as normal acromegaly, being free from both these disturbing elements, the prognosis certainly is very favorable. Years of observation have failed to reveal any local changes in the pituitary or constitutional symptoms denoting any variation from the normal in these cases. In the pathological acromegalics, the prognosis is undoubtedly worse than in the hypopituitarisms of the anterior lobe of this gland, or even in the inactivity of both, in the bilobar cases. Those cases with neoplasms have necessarily a worse prognosis than those without. Even early surgical interference does not offer a good prognosis in these cases. The majority of them have a tendency to recurrences of the original growth and intracranial, as well as hormonic, signs. These recurrences are probably delayed and lessened in severity by postoperative *x*-ray and radium treatment, if this is given early and persistently, following such operations.

Pathology.—The pathology of this case cannot be given in detail, inasmuch as it is not controlled either by operation or autopsy. Being classed in the aneoplastic subdivision, it is supposed to be due to a simple hyperplasia of the anterior lobe, which has not developed to the adenomatous makeup of tumor found in those cases of pituitary neoplasm. The classification of both macroscopic and histological pathology of hypophyseal tumors have been given in Part I. The pathological changes in other portions of the body refer particularly to the short and the flat, peaked bones and to the genitalia. The marked overgrowth of these bones has been previously described in detail. The genitalia during the active stage of the anterior lobe show the general overgrowth of structures of all the organs. This is particularly demonstrable in the gonads of the male, in which there is a hyperplasia of both the seminiferous tubules of Sertoli and the interstitial cells of Leydig. It is more than likely that this corresponding hyperplasia is found in the tissues of the ovaries, although it has been difficult to prove this absolutely by histological specimens. Among the other pathological changes, the writers have noted that nearly all the cases of both gigantism and acromegaly have some objective enlargement of the thyroid. While the changes in this gland are slight, they are usually present to a sufficient degree to make them easily observed, even in the well developed, short necks of these individuals. This case did not have a typical thyroid heart, as is present in some of these individuals and also in different types of giants. The nervous makeup of these individuals, the fast pulse, tendency to hyperpyrexia, tremor, excitation, etc., all speak for a hyperactivity of this gland, if its function is at all involved. There is no evidence in this case of thymic, adrenal, pineal, pancreatic, or other endocrine involvement. The literature proves that when these glands are affected, they are usually hyperactive, with the possible exception of the thymus and the pineal gland, which may either be normal or have absolutely no function. The heart and arteries in these cases are usually well developed and do not have the marked overgrowth present in the giants. The overdevelopment of the osseomuscular system has been spoken of above. There usually is a very decided lack of adipose tissue throughout the entire body, unless late hypo-activity of the posterior lobe occurs. In this case the blood did not show hyperglycemia, and the sugar test demonstrated the absence of marked change in the carbohydrate tolerance. The skin in these cases is practically unchanged, and the organs of special sense are not affected locally, although their functions, particularly of the senses of sight, smell, and taste, are frequently greatly disturbed. Secretions and excretions are not modified in this condition.

SECTION 13

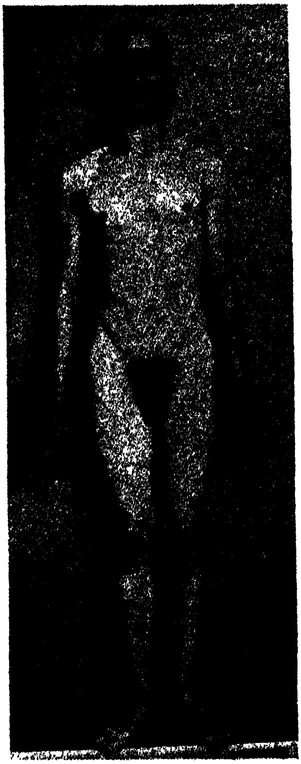
PITUITARY POLYURIA (DIABETES INSIPIDUS)

(*Posterior* [*Pars Intermedia?*] *Lobe Pituitarism, Postadolescent, Aneoplastic Type*)

Etiology.—The disease is comparatively rare. Eichorst saw only 17 cases out of 35,942 patients in the Medical Clinic at Zürich, between 1876 and 1877. Gerhardt found 55 cases among 113,600 treated at the Charité, Berlin, from 1877 to 1896, Futcher, 7 cases out of 403,505 cases treated in the Johns Hopkins Hospital and Dispensary, from 1899 to 1904, the total averaging only 14 cases per 100,000. The writers collected a group of 11 cases from a series of approximately 1,000 patients showing definite clinical evidence of endocrine disturbance. Stoermer found that the disease occurred in men more commonly than in women, and Kulz that it was more frequent in boys than in girls. The familial character has been stated by Clay, Gee, Lancereaux, and Weil, the last named reporting 17 cases in one family in three generations. In the writers' series there were ten men and one woman, the age incidence being between fourteen and thirty-five, with no suggestion of a familial tendency. Analysis of this series with regard to incidence demonstrated the already known fact that the syndrome occurred more frequently in the male, and that it was more prevalent in early life, all the cases of the group having begun before the age of twenty-eight. Heredity could not be held accountable in the series as a predisposing factor. In only a few cases, for example, those having pituitary tumor and those displaying clinical evidence of gigantism and acromegaly, did the family history play an important rôle. Infectious disease and cranial trauma occurring in early adult life were probably etiological factors. In the writers' series of cases, the outstanding features of prominence from an etiological standpoint were (1) cranial trauma, (2) pituitary neoplasm, and (3) infectious disease. The infectious diseases considered of marked importance were mumps, measles, typhoid fever, diphtheria, scarlet fever, and pneumonia. Throughout the entire gamut of pituitary disorders, typhoid fever has consistently been an outstanding etiological factor; but in the particular disease under consideration, parotitis has been commonly noted. In the case under consideration there was a history of both measles and mumps, the attack of mumps occurring in rather definite association with the onset of the symptomatology. In regard to the incidence of pituitary tumor, it was noted that frequently the syndrome preceded by a number of years the onset of the classical neoplastic symptomatology. In one case there was no evidence of pituitary tumor until four years after the onset of a classical diabetes insipidus.

Symptomatology.—HISTORY: CASE XXVI.—Mr. F. B., aged twenty-eight, St. John's Hospital, General No. 1203.

Present.—The symptomatology began a year and one-half prior to the first observation, with general nervousness, insomnia, chilly sensations, lack of concentration, polyuria, polyphagia, and polydipsia, headache, nausea and vomiting, abdominal distention, constipation, and increased libido, as manifested by frequent nocturnal emissions. The patient gives a history that at the age of twelve, polyuria, albuminuria, and glycosuria were found. The urinary output at that time reached 6,000 c.c. in twenty-four hours. From that time until the age of fourteen the patient complained of being sick most of the time, the chief complaints being weakness, nervousness, anorexia, recurrent furunculosis, abdominal cramping, diarrhea, and occasional slight temperature. Sugar was never again demonstrated in the urine. Between the ages of sixteen and twenty, the patient was in fairly good health, of normal



CASE XXVI. FIG. 1.—NOTE EUNUCHOID TYPE, WITH OVERDEVELOPMENT OF LONG BONES; LONG HANDS, WITH SLENDER, TAPERING FINGERS.

weight and height. At the age of twenty consistent loss of weight began, although the patient was subjectively well. Since that time he has been gradually losing weight, and for the past two or three years has complained of not feeling well, enumerating as the chief complaints nervousness, insomnia, polyuria, polyphagia, polydipsia, fatigability, headache, nausea, and vomiting, which series of symptoms has been growing in intensity throughout the past two or three years.

Past.—Measles, mumps at the age of eleven (without orchitis).

Personal and Family.—Negative.

EXAMINATION.—*General.*—Lower measurement, 38 inches (96 cm.); upper, 34½ inches (87½ cm.); span, 78 inches (198 cm.). Tall, slender, eunuchoid type of individual. Very slight growth of hair about thighs and upper portions of legs, lower legs comparatively free. Absolutely no abnormal hair growth about upper portion of body. Hands very long, palms narrow, fingers long and tapering, lunular markings visible. Distance from wrist joint to tip of middle finger, 8⅝ inches (22 cm.); from knuckle to tip of middle finger, 4¾ inches (12 cm.); circumference of palm at widest position, 8⅝ inches (22 cm.); length of arm from elbow to lower end of radius, 11⅞ inches (30 cm.). Feet of same general character as hands, very long. Size of shoe, 10½, medium last. Faint brownish pigmentation about forehead, extending down on lateral aspects of cheeks and neck. No scars or lesions about body except brownish scar on right anterior leg (old infection following bruise). Skin of body warm, with exception of feet. Pulse slow, regular, 60-80. Blood-pressure, 120/85. Temperature constantly subnormal, 96°-98° F. (35.6°-36.7° C.).

Regional.—Negative with exception of proportionate overgrowth of all bones.

LABORATORY FINDINGS.—*Urine.*—(See Fig. 2, Case XXVI.) 3,000-4,800 c.c., specific gravity 1.000-1.010, free from *albumin, sugar,* and morphological elements.

Blood:

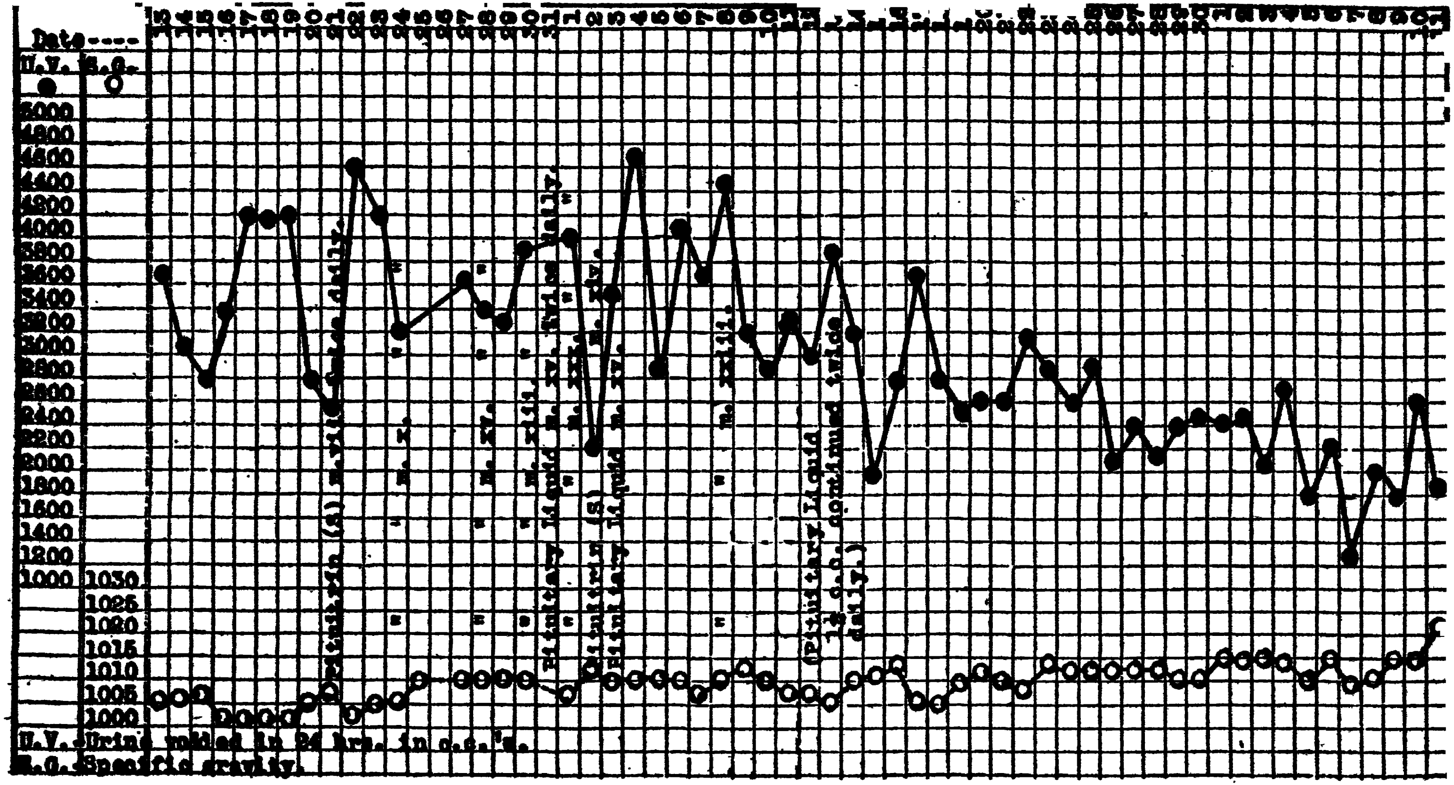
Erythrocytes	4,800,000
Leukocytes	9,800
Hemoglobin	104 per cent.
Stained smear	normal
Wassermann	negative

Carbohydrate Tolerance.—Normal: Blood-sugar after 15 hours' fast, 0.13 per cent. (normal, 0.10-0.12 per cent.); one hour after the ingestion of 123 grams dextrose, 0.156 per cent. (normal, 0.18 per cent.); two hours after ingestion, 0.112 per cent. (normal, 0.15 per cent.).

Basal Metabolism.—Three per cent.

Stomach Analysis (Ewald breakfast).—Free hydrochloric acid 15, combined acidity 7, total acidity 22; microscopical examination gave normal findings.

SPECIAL FINDINGS.—*X-ray.*—*Sella turcica small,* anteroposterior diameter 10 mm., depth 5 mm. *Fluoroscopic examination of stomach and*



CASE XXVI. FIG. 2.—GRAPHIC CHART SHOWING AMOUNT AND SPECIFIC GRAVITY OF URINE VOIDED, AND INFLUENCE OF PITUITRIN AND PITUITARY LIQUID.

colon normal. Roentgenogram of chest negative. Roentgenogram of hand shows no definite tufting of exostoses, slight overgrowth of metacarpophalangeal bones.

SUBSEQUENT COURSE.—(See Fig. 2, Case XXVI.) The patient entered St. John's Hospital October 12 and was dismissed December 12, 1918, during which time he was given **pituitary substance** (entire gland), grains x (0.65 gram) after meals, and increasing doses of **pituitary liquid,** from minims vii to minims xxx (0.42 to 1.9 c.c.), twice daily. The total amount of urine dropped from 4,800 to between 1,600 and 2,000 c.c., the specific gravity increasing from 1.000 to between 1.015 and 1.020. The headaches, nausea, vomiting, and muscle fatigue disappeared entirely. The patient was then dismissed from the hospital and placed upon pituitary substance (entire gland) grains v (0.324 gram) three times daily after eating. During the following six months there was no recurrence of polyuria, polydipsia, polyphagia, nervous or gastric symptoms. For the following one and one-half years all treatment was discontinued. There was only an occasional recurrence, particularly when the patient was under tension or strain, at which time he would have transient polyuria, polyphagia, and polydipsia for a few days, associated with nervousness and fatigue. At the end of this time he was again given pituitary substance grains x (0.65 gram), three times daily, and a few hypodermic injections of **pituitrin,** which controlled the tendency to transient relapses, even when he was working under tension, and improved his general condition. For the past two years the patient has been intermittently under observation, and has shown practically none of the original symptoms. He is a highly intelligent individual and keeps close watch upon the manifestations of the disease. Frequent accurately measured twenty-four-hour specimens showed a twenty-four-hour output ranging from 1,900 to 2,000 c.c. There is absolutely no gastric disturbance, no headache, and none of the general complex or nervous symptoms. The patient is taking pituitary substance intermittently by mouth and a very occasional hypodermic of pituitrin (0).

Diagnosis.—The diagnosis in this case is secretory dyscrasia of the posterior lobe of the pituitary gland, the pars intermedia being considered a part of this lobe of the hypophysis. There is slight clinical evidence of anterior lobe involvement, inasmuch as the individual shows rather decided overdevelopment of the long bones. There is no evidence of posterior lobe deficiency in the way of increased adiposity, etc. The diagnosis is based upon the following points: (1) persistent polyuria, associated with polydipsia and polyphagia; (2) marked general nervousness, headache, nausea, vomiting, and abdominal disturbance; (3) exclusion by differential diagnosis of other diseases. The polyuria was an early symptom and at one time supposedly associated with glycosuria, although this latter feature was never verified. The onset was rather gradual, and apparently bore some relationship to an attack of infectious parotitis. The amount of urine passed daily, as given in the history, ranged from 3,000 to 4,800 c.c., an amount smaller than ordinarily occurs in a typical diabetes insipidus. This polyuria was definitely associated with polydipsia and polyphagia. The urinary examination disclosed a specific gravity ranging from 1.000 to 1.010, a varying reaction, and a complete freedom from albumin, sugar, and pathological microscopical findings. The blood-pressure registered systolic 120, diastolic 85. The functional kidney tests were within the normal. The above findings and associated renal signs are within the limits of the ordinary clinical manifestations of diabetes insipidus. That the polyuria is one of the most dependable early signs of dysfunction of the posterior and intermediate lobes of the hypophysis is now considered fairly well established. Whether all cases of diabetes insipidus, however, are due to secretory dyscrasia of the posterior or intermediate lobe is very much of an open question. The consensus of opinion regarding this point tends to prove that more than likely the posterior lobe of the hypophysis is involved either directly or secondarily in the majority of these cases. So constant has been the association of pituitary tumor or signs of disturbed function of some lobe of the hypophysis with polyuria, that the authors have deemed it not out of place to term this condition pituitary polyuria, in order to more readily appreciate the connection of the syndrome with this endocrine gland.

The pathogenesis of this clinical syndrome will be discussed under the heading Pathology. The more recent inclination has been to attribute the polyuria exclusively to the function of the pars intermedia, instead of to the posterior lobe proper. The writers, as has been noted in preceding sections, have considered the pars intermedia as a part of the posterior lobe. The confusing problem of whether this syndrome is due to a hypo- or a hypersecretion of these portions of the gland will be considered in detail under Pathology. In the writers' series of cases there was a definitely consistent symptomatology, consisting of polyuria, polyphagia, polydipsia, marked general nervousness, intracranial symptoms, headache, visual disturbance, increased irritability, disturbance of gait, etc. Most of these classical features are exemplified in the case reported above. The cranial symptoms are among the most common present in pituitarism. Review of the histories previously given, or those of other positive case reports, will demonstrate that these *peculiar headaches, located around the base of the skull,* sometimes anteriorly, sometimes posteriorly, and frequently laterally, are a constant feature in the description of these diseases. The *ocular disturbances* are very characteristic, and vary from minor subjective irritative sensations about the eyes or eyeballs to complete hemianopsia. Zentmayer has summarized the present-day information regarding the effects of the endocrine glands upon the system, with special reference to the effect upon the eyes. His comprehensive paper corroborates much of the writers' personal experience reported in previous cases. He gives considerable attention to the glandular treatment of the ocular condition, a subject which to date has received comparatively little attention. Photophobia, associated with orbital discomfort and pressure sensitiveness of the eyeball, is frequently present. It has been previously restated, however, that localized or complete bilateral blindness occurs in only a small percentage of pituitarisms having neoplasm causing actual pressure. In these cases it does not consist of the classical temporal hemianopsia so graphically described in the texts. There are very few cases of any state of activity of the pituitary involving either one or both lobes, which do not have some ocular symptoms. For instance, over *90 per cent.* of the writers' cases of *hypopituitarism,* many of which had a *smaller sella turcica than normal, had very definite ocular symptoms,* which were undoubtedly related to the pituitary disease. Many of these patients have been proven by competent oculists to be *absolutely free from eye lesions* or *refractive errors.* In those cases in which refractive errors of varying degree are found, it is very rarely that the eye symptoms are relieved by the proper correction of these errors. The association of the *headaches* with *ocular signs,* and particularly the relationship of the headaches to *eye fatigue,* have probably been very misleading to oculists who find an error of refraction in these individuals and offer a good prognosis upon its proper correction. Cushing has attributed the headaches and other cranial nervous phenomena in these diseases of the aneoplastic type to possible tension of the capsule of the pituitary gland. He obtained complete relief from this headache in 2 cases by means of sella decompression, by splitting the capsule of this gland, which had been shown previous to operation to be only moderately enlarged. The general nervous symptoms in this case, consisting of high nervous tension, irritability, subjective vertigo, etc., have been so frequently elicited in other positive cases as to be of more than minor significance. A small sella and the absence of pressure signs upon the optic, third, fourth, or sixth nerve, or other structures in the neighborhood of the pituitary, proved that, if there was an enlargement of this gland, it was so slight as not to produce definite intracranial pressure signs.

Differential diagnosis would involve those diseases having *cephalalgia, psychoneurosis,* or *polyuria* as one of the presenting symptoms. Differentiation of headaches, either of local or general origin, cannot be considered in this discussion. All those due to diseases of the eyes, sinuses, or teeth; infectious indurations of the tendon attachments of the skull; headaches from scalp, skull, and intracranial lesions; headaches due to general, such as luetic or pyogenic, or focal infections; and headaches associated with diseases of other organs, as the kidneys, colon, etc., must be given consideration. In the majority of these cases other cranial lesions have been excluded by competent examinations and corrections of diseases of the eyes, nose, throat, teeth, ears, mastoids, etc., before they consult the internists for diagnosis. A great many of them have also been treated for chronic constipation and renal disease, on account of the prevalence of symptoms referable to these organs. The diagnosis of *psychoneurosis* can also frequently be excluded by the prolonged treatment to which many of these patients have been submitted for such disease, without benefit. For instance, the writers have a number of pituitarisms which have undergone prolonged hygienic, hydrotherapeutic, psychic and rest cures, in well-regulated sanitaria devoted especially to this type of patients, who have received absolutely no benefit from such treatment. *Chronic nephritis,* particularly that due to chronic interstitial and secondary contracted kidneys, is one of the diseases which it is necessary to differentiate from these hyposecretions of the posterior lobe of the hypophysis. On account of the amount and character of the urine, the high blood-pressure, the headaches, and the cardiac changes, the disease very frequently mimics this type of renal lesion. The functional kidney tests, the absence of excessively high blood-pressure, and other hormonic signs of pituitary disease, are usually sufficient to make this differentiation. True *diabetes mellitus* can easily be differentiated by the absence of glycosuria and hyperglycemia. It is of course deemed unnecessary to discuss in a differential way the intermittent and chronic polyurias of other types, such as those due to excessive drinking, absorption of transudates and exudates, hydronephrosis, bladder obstruction, contracted kidney, reflex hydruria following ureteral catheterization, urina spastica of migraine, epilepsy, etc.

Complications, Sequelæ, and Associated Diseases.—There are no definite complications present in this case. During the entire observation there was no evidence of decided inactivity either of the anterior or the posterior lobe, although the pars intermedia, according to the most advanced theory, was underfunctioning. It has been interesting to note that obesity, a characteristic hormonic sign of hyposecretion of the posterior lobe, has been absent in most of the writers' series of cases, although the association of dystrophia adiposogenitalis (Fröhlich's syndrome) with polyuria has been reported in the literature by Biedl, Fearnsides, Marañon and Pintos, and Schünemann. Theoretically, upon the assumption that dystrophia adiposogenitalis is due to insufficiency of both the anterior and posterior lobes, and that polyuria is due to a hyposecretion of the pars intermedia, the association should be more common. There is no evidence in this case, or in any of the series, of special susceptibility to other diseases. In this sense, the writers' cases of diabetes insipidus, presumably deficiency of the pars intermedia, differ from the classical cases of posterior lobe hyposecretion, inasmuch as the latter have been, in their experience, very susceptible to intercurrent infections.

Clinical Varieties.—A proper conception of the possibilities in the clinical variation of the associated manifestations of diabetes insipidus necessitates an appreciation of the individuality of the component lobes of the hypophysis and of the fact that they may be harmoniously hypo- or hyperactive, or that they may be hetero-active. For instance, we may find the clinical presentation of the dystrophia adiposogenitalis representing a hypo-activity of both the anterior and the posterior lobes of the hypophysis, associated with a polyuria, presumably a hypo-activity of the intermediate lobe, thus representing a harmonious trilobar hypoactivity. Again we may find the association of acromegaly, representing a postadolescent *hyperactivity* of the anterior lobe, associated with anterior lobe, coincident with a hypo-activity of the intermediate lobe, thus giving us an example of hypophyseal *hetero-activity,* taking into consideration, of course, the fact that the gross skeletal changes of anterior lobe hyperactivity may have been transient and that the present state may in reality be a transformed one, or a hypo-activity of the anterior lobe, coïncident with a hypo-activity of the intermediate lobe, as reflected clinically in the polyuria. With true appreciation of the possibilities of harmonious hypo- or hyperactivity and of hetero-activity, the clinical associations of polyuria are necessarily numerous and complex. We feel that an appreciation of the hormonic signs as expressed above will enable the reader to recognize the possibility of the various combinations.

Upon the basis that this polyuria and associated symptoms are due to pituitary disorder, it is most interesting to analyze those positive signs or symptoms, other than the increased diuresis and nervous symptoms, present in the authors' series of 11 cases, which are definitely related to a pituitary dyscrasia. Of these cases, 5 had no definite osseous, adipose, or general changes, or other hormonic signs which would relate them specifically to pituitary disorder. On the other hand, 6 had very striking pituitary signs other than the polyuria and nervous manifestations. Two were pituitary tumors, in which the polyuria was the initial and early sign. One had other signs of pituitary disorder, evidenced by the easily discernible osseous changes of *acromegalic gigantism,* having all the classical symptoms of acromegaly and gigantism associated with poth pre- and postadolescent hypersecretion of the anterior lobe of the pituitary gland. Two had, besides the pituitary polyuria complex, the classical hormonic signs produced by hypersecretion, during preadolescence, of the anterior lobe of the pituitary, responsible for the eunuchoid gigantism. In both these cases, other signs of disorder of the pars nervosa, such as glycosuria, hyperglycemia, and adiposity, were absent. In one case there were classical markings of acromegaly present with the onset and throughout the course of the polyuria (from the age of twelve to thirty-seven). In this case, *after a polyuria of twenty-five years' duration,* there occurred a glycosuria, hyperglycemia, and decreased sugar tolerance. This case then presented evidence of associated anterior lobe hyperfunction (acromegaly) during its initial course, and a related hyperfunction (glycosuria and hyperglycemia) of the pars nervosa during the late course of the polyuria.

Treatment.—The many cases reported in the literature which have reacted to **pituitrin** (the extract of the posterior and middle, or infundibular, lobes of the hypophysis) have established a new era in the treatment, as well as in the etiology and prognosis of this disease. While it is true that nearly all investigators have found this pituitrin treatment beneficial in the majority of cases, yet it is the opinion of the writers that it is not a specific, or even effective in all cases. In those cases in which it does produce marvelous changes in the symptomatology and course of the disease, the majority of investigators are free to admit that, unless it is continued indefinitely, there is tendency to relapse, and that an interruption of treatment for any length of time frequently exposes the patient to a return of all the symptoms of the disease. Only in one case of the above series, after the syndrome had been completely relieved by subcutaneous treatment, was the patient able to continue on pituitary treatment by mouth without a return of the symptoms. In this case, after he discontinued the oral administration of pituitary substance, there was a return of both the polyuria and nervous manifestations, although in a much milder form than those present previous to the initial treatment. The other 5 cases which reacted satisfactorily to intensive pituitary treatment had a constant tendency to relapse as soon as there was a reduction in the tolerant dosage of this substance. The fact that all these cases do not react to this treatment, however, and that even those which do react may relapse if the treatment is discontinued, should not prevent the application of this form of therapy. The definite determination of the pathogenesis of this disease and its more favorable therapeutic response will depend to a large extent upon such clinical investigation as the very careful observation of the therapeutic reaction to pituitrin and possibly to other ductless gland preparations in cases of pituitarism in polyglandular syndromes.

Another very important estimation to be accurately noted in the administration of pituitrin to these patients, which will undoubtedly help to clarify both etiology and treatment, is the careful measurement of the amount of pituitrin which each individual will tolerate without the production of physiological effect. The writers have recognized and reported three types of physiological reaction, the "intestinal," the "vascular," and the "general." The *"intestinal"* reaction to pituitrin evidences itself by a cramping, colicky sensation in the abdomen, succeeded within a few minutes by bowel evacuation. This intestinal reaction usually begins within five minutes and rarely occurs later than fifteen minutes after the injection of a sufficient amount of pituitrin. The average individual having a normal secretion of the posterior lobe and pars intermedia will obtain this reaction after the administration of from x to xv minims (0.6-0.92 c.c.) of pituitrin (0). Doses which do not produce this reaction are considered insufficient to be effective in substituting for the normal amount necessary to the individuals possessing deficient hypophyseal secretion. It has been thought that the size of the dose producing this reaction might be used as a diagnostic means of determining the degree of insufficiency of the pars intermedia and posterior lobe of this gland. In other words, in those individuals having a marked decrease in secretion, productive of the symptomatology of pituitary polyuria, it should require a much larger dosage than in a normal individual to produce the constriction effect upon the intestinal unstriped muscle. In the writers' histories it has been noted that this was true in those cases which later reacted to pituitrin treatment. The writers have also found a positive pituitrin reaction in many bilobar insufficiencies of the pituitary gland, without polyuria, such as typical Fröhlich's disease. In some of these cases it takes two or three times the amount of pituitrin required in a normal individual to produce this response. This same intestinal reaction is produced by a large amount of extract of the posterior lobe of the pituitary gland by mouth. The oral administration has the advantage of avoiding an undesirable local reaction, but has the disadvantage of being very expensive because of the large amount required to produce an effect equal to that received by subcutaneous use.

The "*vascular*" reaction consists of transient pallor, usually appearing within three or four minutes after hypodermic administration and rarely lasting more than five minutes. A prolongation of this vascular reaction, to which are added severe nervous symptoms, has been defined the "*general*" pituitrin reaction. The general reaction consists of tachycardia, syncope, and extreme emotionalism, associated with prolonged pallor. This reaction is considered a toxic or untoward one and should be avoided when administering this substance. It is rarely the result of a smaller dose than that which produces the intestinal reaction, but should it occur before the intestinal reaction, the indications would be to decrease the size of the dosage and not to attempt to give one sufficient to produce the intestinal response. The occurrence of the vascular reaction should caution one to observe the patient for a short time to see that this effect passes away without additional signs of tachycardia, syncope, or emotionalism. In order to do this, the patient receiving pituitrin should be detained under observation for at least fifteen or twenty minutes after injection, so as to determine what reaction occurs. If the vascular reaction of pallor alone occurs, and disappears without additional signs of general reaction, the patient may be dismissed without danger of this untoward and alarming reaction occurring later. If, after giving an injection of this substance, however, the vascular reaction, in the form of extreme pallor, persists, there is likelihood that other signs of the general reaction will occur. If the vascular reaction lasts longer than a few minutes, the patient should not be allowed to pass out from under personal observation, for fear that serious symptoms will occur, which in certain instances might even lead to disastrous results, such as cardiac or cerebral accident. With this knowledge of the possible toxic effects of pituitrin as a guide to their prevention, one is safe in administering this medication.

The amounts of pituitrin producing these different reactions should be noted, so as to help in determining the amount of insufficiency of this gland, as well as to measure accurately the dose necessary to overcome this hypophyseal deficiency. It has been the writers' custom in adults to begin with a dose of pituitrin (0), minims v (0.3 c.c.), and gradually to increase by 1 minim (0.06 c.c.) each day until the intestinal reaction is produced. This dosage is then considered the tolerant physiological dose sufficient to overcome the insufficiency of the gland. In infants and children, 1 minim, or, if below one year of age, a fraction of a minim, is used as the initial dose. When this extract is given by mouth, the adult is started with minims xv to xx (0.2 to 1.25 c.c.) a day, and the dosage increased by minims ii to iii (0.12 to 0.18 c.c.) each day until the intestinal reaction above described is obtained. This dosage is then continued, and careful observations are made of the polyuria, headaches, nervous disturbances, etc., for a number of weeks, to determine its effect upon the symptoms. If, after two or three weeks of intensive treatment, with a carefully measured tolerant dose, there has been no decided effect upon the chief complaints, the case is considered one not reacting to treatment. Besides the hypodermic administration of pituitrin extract, the *entire gland substance* is given by mouth, pituitary substance in dosage of grains 10 to 30 (0.65 to 1.95 gram) after meals. The writers have never observed intestinal, vascular, or general reactions from the oral administration of this substance. It is understood that substitution of pituitrin or pituitary substance, as described, is indicated only in those cases in which there is definite hyposecretion or insufficiency of the infundibulum or of the posterior lobe of the hypophysis.

In those cases in which this syndrome is associated with the opposite activity, *i. e.*, a hypersecretion or overfunction of the gland, this substitution treatment would be contra-indicated. Pituitrin treatment in such cases would undoubtedly aggravate all symptoms, and consequently might be dangerous. For this reason it is well first carefully to note the effect of even smaller doses of this extract. If there is any definite increase in polyuria, headaches, or nervous symptoms, treatment should be interrupted at once and given in much smaller doses under careful observation, in order to confirm such a reaction. If it can be established that definite hypersecretion is present, the treatment which would be indicated is one calculated to reduce the already increased secretion and oversupply of this substance in the body. The only agents which are available in these conditions are: (1) *x*-ray, (2) radium, (3) glandular substances physiologically antagonistic to the hypophysis, and (4) surgical procedures. As regards the efficacy of *x*-ray treatment in hypophyseal conditions, Schaefer reports 8 cases of tumor of the hypophysis, with acromegaly, treated by this means, 6 showing definite improvement. He accentuates the fact that the head should be so placed that the hypophysis is situated in the focus of the rays. Webster reports a case of early acromegaly in which sixteen treatments with hard filtered rays, through the temporal and frontotemporal areas, were given with good results. The first eleven of these treatments were given at weekly intervals. Jaugeas was successful in the use of *x*-ray treatment in tumors and hyperactivities of the hypophysis, and states that the change in the visual fields parallels the benefit and forms a gauge to the efficacy of treatment. Cavazzini-Bergamo reports 2 cases of hypophyseal tumor with acromegaly which were greatly benefited by *x*-ray treatments by the Beclerc method—deep roentgenotherapy through the two temporal and frontal regions, at first every week, later less frequently. One case of the writers' series did not react to *x*-ray therapy. As regards the use of **radium**, theoretically this form of treatment should be possible, either by external or suitable endonasal or endopharyngeal application. We have no clinical data concerning the efficacy of this form of treatment. Certain investigators have ascribed to certain glandular preparations—notably, **extract of placenta**—anti-hypophyseal effects. The earlier results in this field of endeavor have been unfruitful. **Surgical procedure** is a well-recognized method of treatment, leaving room for some argument concerning the best method of approach, as each technical modification has its own adherents.

Prognosis.—The results of treatment, particularly of pituitrin, demonstrated that in 5 cases this preparation exerted a decided influence upon the polyuria and other symptoms. In 4 cases, including 2 neoplasms, pituitrin was not instituted. In 1 case this treatment had absolutely no effect upon the polyuria or other symptoms. In this case there was an associated disorder of the anterior lobe, producing eunuchoid gigantism, which might account for the lack of response to pituitrin treatment. A similar case, however, did react completely to this treatment. In one case it had an opposite effect, not ordinarily expected, namely, the production of an increase in the polyuria and associated symptoms. In this case there was clinical evidence of hypersecretion of the posterior lobe, associated with glycosuria, hyperglycemia, decreased sugar tolerance, and acromegaly. In one case adrenalin seemed to greatly intensify the polyuria, and in another it was impossible to note any effect due to adrenalin or suprarenal substance, either upon the polyuria or associated symptoms. In this same case extract of placenta, a combination of anterior and posterior lobe extracts, orchitic substance, thyroid gland, and combinations of these different ductless gland preparations, had no effect upon any of the symptoms. Cocain solution was tried upon 2 cases, with practically no influence in activating or decreasing the symptoms. Spinal puncture and *x*-ray radiations (ten exposures) of the hypophysis, applied to the refractory case described above, which did not react to any ductless gland therapy, had absolutely no effect in ameliorating any of the symptoms.

Deductions from an analysis of this series of 11 cases show that in practically 50 per cent. there was evidence of decreased function or activity of the pituitary gland, affecting probably the pars intermedia. These conclusions are deduced: (1) from the fact that not all cases have other evidence of anterior or posterior lobe disorder, as shown by the 5 cases described above, and (2) from the observation that only 50 per cent. of the cases were improved by pituitrin treatment. Why one classical case was not at all affected by pituitrin treatment is difficult to explain, except on the ground that it is a bilobar case, having anterior lobar, in addition to pars intermedia, involvement. The fact that the polyuria associated with the acromegaly was not relieved by pituitrin treatment might also have been due to the specific activity of other lobes of the gland, for in this case there was decided involvement of both the anterior lobe and the pars nervosa, as shown by the classical signs present resulting from disturbed function of these other portions of the gland. These 2 cases, however, help to contend against the theory that all cases are due to hyposecretion or decreased function of the posterior lobe or of the pars intermedia of this gland, and demonstrate that there is a considerable amount of uncertainty regarding the activity of the hypophyseal lobe producing this interesting syndrome.

Pathology.—The development of the pathogenesis of this dramatic clinical syndrome has been one of the most fascinating studies in medicine. In 1682, Thomas Willis noted that the urine of some diabetic patients was sweet, and that of others was not, which fact led him to introduce the classification of saccharin and non-saccharin diabetes. In 1794, Johann Frank defined the condition as diabetes insipidus, or spurious diabetes, as distinguished from diabetes mellitus, or true diabetes. Since this time there have been many theories, and a tremendous amount of literature has accumulated regarding the causation and pathology of this disease. Three commonly propounded theories are: (1) that the disease is due to faulty concentration of urine on the part of the kidneys; (2) that it is a primary polydipsia, with normal renal function; and (3) that it is a symptomatic polyuria induced by stimulation of the kidney from different causes, the older theories being of functional and organic nervous lesions, the more notable and recent pathogenesis being due to a disorder of hypophyseal secretion. However, no definitely consistent pathology of the disease has been established. Tallqvist, E. Meyer, Seiler, and Socin thought the condition due to lack of ability of the kidney to secrete a concentrated urine. Finkelnburg, Schwenkenbecher, Falta, Forschbach and Weber did not believe that the concentrating power of the kidney was lost, but that there was a pathological stimulation which produced larger amounts. Spaether considered diabetes insipidus to be a paresis of the renal vasomotor nerves, of either central or peripheral origin. Ebstein was of the opinion that the condition was due to primary polydipsia, with resultant polyuria.

Although many cases of diabetes insipidus carefully studied showed no pathology, many others displayed definite lesions about the floor of the fourth ventricle or in the hypophysis. Claude Bernard, in 1849, proved that if the medulla oblongata and the brain-stem were punctured in various places, a definite polyuria would occur. In 1870, Eckhard produced polyuria by various types of irritation of the vermiform process of the middle lobe, and injury to the posterior lobe of the brain. Kahler, in 1886, produced a permanent polyuria and polydipsia in animals by injecting small quantities of concentrated silver nitrate solution into various portions of the brain.

In the course of these investigations, the hypophysis naturally demanded considerable attention. Schaefer first demonstrated that the administration of posterior lobe extracts produced a marked polyuria in animals. Schaefer and Oliver, and Magnus and Herring later confirmed this fact. E. Frank and Cushing noted the frequent association of the condition with lesions of the base of the brain, particularly involving the hypophysis. Schaefer found a polyuria due to non-bloody mechanical or chemical irritation of the hypophysis. Crowe, Cushing, and Homans noted the presence of a polyuria after operations upon the pituitary gland in animals, and the same occurrence and disappearance of polyuria following operations upon hypophyseal tumors in man. These clinical and experimental facts led to the conclusion that diabetes insipidus was due to a hyperfunction of the posterior and intermediate lobes of the hypophysis. This opinion obtained for a time, although many discrepancies were noted, both clinical and experimental, and the trend of opinion began to swing from the hypersecretory hypothesis to hyposecretion of the posterior and intermediate lobes of the pituitary.

The first significant work in support of the latter view was done by Pentimalli and Quercia, in 1912, who found, in contradiction to Schaefer's work, that in the perfused, isolated kidney of the rabbit, extract of the posterior lobe caused *constriction* of the renal vessels, and that diuresis was diminished instead of increased. In 1913, Farini and von der Velden published the fact that extract from the hypophysis would decrease the amount of urine in cases of diabetes insipidus, as well as in healthy individuals. In 1914, Motzfeldt demonstrated the same fact by the injection of pituglandol (extract from the posterior lobe and pars intermedia), and was of the opinion that the original experiments of Magnus and Schaefer were faulty, due to the fact that they had used anesthetized animals. Motzfeldt, in his own work, used rabbits without anesthesia. Polyuria would follow the introduction of water into the stomachs of these rabbits and could be absolutely controlled and decreased by the subcutaneous injection of posterior lobe extracts. This effect was constant, and seemed to be independent of intestinal absorption and vagal influence. It could be prevented by section of the splanchnics or of the renal nerves near the hilum of the kidney. He concluded that the secretion of the pars intermedia exerted its antidiuretic effect in the stimulation of the sympathetic nerves, influencing especially the renal vasomotor system. He reported 3 cases in which nothing abnormal was found in the pituitary, but in which a number of symptoms pointed to an insufficiency of the posterior lobe. Bab believed the hypophysis to be a regulator for the control of the physiological functions of the urogenital system, and considered diabetes insipidus to be (1) a hypofunction of the pars intermedia, (2) a disturbance of the reception of the secretion in the pars posterior, or (3) a propagation of the secretion in the cerebral lacunæ. Many clinical discrepancies had been noted, for example, as remarked by Biedl, the association of diabetes insipidus with dystrophia adiposogenitalis. These considerations led to a reversal of opinion, the consensus being that diabetes insipidus was due to hyposecretion of the pars intermedia and pars posterior. Numerous reports followed, dealing largely with the therapeutic effect of various forms of pituitary extract upon the polyuria. These reports include articles by Roemer (1913 and 1914), Biach (1914), Frey and Kumpiess (1914), Umber (1914), Falta (1915), E. Graul (1915), Hoppe-Seyler (1915), Kleeblatt (1915), von Konschegg and Schuster (1915), Strauss (1916), Bab (1916 and 1917), and G. Marañon (1917). Barker and Mosenthal, in 1917, reported 2 cases in which the polyuria was markedly controlled by the injection of pituitrin and pituitary liquid. They state that the urine was diminished in amount, the specific gravity increased, and the percentage of sodium chlorids and nitrogen content increased by the injection of extract of the pars posterior and pars intermedia. Tethelin (anterior lobe extract) and adrenalin were of no value. They believe the kidneys to be healthy in diabetes insipidus, and hold that the condition is one of deficiency of secretion of the pars intermedia. Barker suggests the possibility that substances closely allied to pituitrin, such as histamin, might be substituted. The similarity of histamin and pituitary extract, in their action upon the uteri of mice and guinea pigs, has been recently expressed by Abel and Macht, while Cow finds opposite effects, leading him to conclude that the plain-muscle-stimulating principle of histamin and that of posterior lobe are not identical. Jackson and Mills likewise find differences.

In addition to the theories concerning hyper- and hyposecretion of the hypophysis cerebri in diabetes insipidus, other investigators have advanced the theory that the hypophysis is not necessarily involved, maintaining that lesions elsewhere about the floor of the fourth ventricle, or in the midbrain, may be productive of the syndrome. The earlier experiments of Claude Bernard, Eckhard, and Kahler, quoted previously, would seem to support this opinion. Houssay does not accept the view that the polyuria is due to a diuretic hypersecretion of the pituitary gland, and states that in his experience the pharmacological action of pituitary extract was so variable that it was not permissible to deduce an insufficiency of the pituitary body from the successful use of the extract in controlling polyuria. He asserts that different immediate effects occur when pituitary extracts are injected intravenously, and that the chemical composition of the gland is very constant, as are the physiological effects of the gland extract, but that these effects vary qualitatively according to the methods of preparation. He states that both renocontractor and renodilator substances occur in the pituitary extracts, one or the other predominating, according to the circumstances, the *diuretic* effect running parallel with the *renovascular* effect. He disagrees with Cushing in his claim that the cerebrospinal fluid contains this substance and produces the same effect as pituitary extract, or that the secretion is poured into the fourth ventricle, as affirmed by Herring. His animal experiments demonstrated that the removal of the hypophysis produced decided differences in adult and in very young dogs. In the adult an oliguria often occurred, while in the puppy polyuria was a constant finding for a few days succeeding operation. He believes that both these changes in urinary output were due to trauma, as these same changes in diuresis were observed in those animals in which the hypophysis was entirely removed. He studied in detail the effect of trauma to the neighborhood cerebrobasal zone and to the pituitary body itself, employing iron filings. It was possible, by means of the *x*-ray, to observe the effects upon dogs for a long time. Injuries within the determined zone produced polyuria. Injuries without the zone did not result in polyuria. Houssay believes that the polyuria was not due to pituitary involvement, but that it was produced by injury to the neighborhood tissues in close proximity to this gland. In one case he punctured the infundibulum and penetrated into the third ventricle, without injuring the brain and without developing a polyuria. He defines the zone within which injury is productive of polyuria as limited posteriorly by the peduncle protuberances, anteriorly by a line near the anterior limit of the optic chiasm, and laterally by the hippocampal gyrus. He does not believe that the pituitary constitutes a part of this zone, although it may be possible that the posterior lobe does participate.

Leschke, while admitting that lesions of the hypophysis, such as trauma, sarcoma, carcinoma, tuberculosis, syphilis, etc., have been demonstrated in cases of diabetes insipidus, claims that similar lesions in the midbrain, especially those involving the tuber cinereum, may produce diabetes insipidus, even when the hypophysis is intact. He regards the hypophyseal lesion as purely incidental, and, if associated with diabetes insipidus, due to pressure or extension of the lesion into the tuber cinereum. J. Camus and G. Roussy contend that experimental data prove that lesions of the tuber cinereum and infundibulum are productive of polyuria. They found that after removal of the hypophysis in dogs, pituitary treatment did not improve the syndrome of diabetes insipidus, from which fact it was inferred that the essential factor might be a lesion of the adjacent zone of the brain. Claude and Lhermitte described a case presenting bitemporal hemianopsia, attacks of dysarthria, amnesia and delirium, attacks of narcolepsy, tachycardia, irregularity of the heart-beat, extrasystoles, embryocardia, increased blood-pressure, polyuria, and polydipsia, in which postmortem examination disclosed a tumor formed from the ventral wall of the third ventricle and distinctly confined to the *infundibulum.* They state that the hypophysis was completely normal. This article attempts to ascribe polyuria accompanied by polydipsia to lesions of the base of the third ventricle, and not to lesions of the hypophysis. M. Olaechea reports a case which led him to subscribe to the infundibular hypothesis. On the other hand, A. M. Luzzato contends that destructive lesions of the neurohypophysis or pedicle may produce the syndrome, with no demonstrable lesion of the infundibulum.

Chiasserini found that hyperplastic changes in the *pars intermedia,* experimentally produced by injections of sporotricha and tubercle bacilli into the sella turcica or hypophysis, resulted in polyuria.

Thus it may be seen that the accumulated data to date, independently of such considerations as local kidney conditions or primary polydipsia, offers a considerable variety of causation: (1) hypersecretion of the posterior (pars nervosa) and intermediate (pars intermedia) lobes of the hypophysis, (2) hyposecretion of the posterior and intermediate lobes of the hypophysis, (3) disorder of the intermediate lobe (pars intermedia), without involvement of the anterior lobe or the pars nervosa of the pituitary, (4) lesions of the hypophyseal neighborhood, without involvement of the hypophysis proper. Of course, it must be recalled, as Simmonds pointed out, that lesions occur in the specified zones without polyuria, and, on the other hand, the syndrome of diabetes insipidus may exist without demonstrable lesions of the hypophysis or hypophyseal neighborhood. Yet it must be borne in mind that the *histological knowledge of the hypophysis to date is so indefinite that no convincing deductions can be based upon it relative to the activity of the secretions or functions of the individual lobes of this endocrine gland.*

SECTION 14

PITUITARY GLYCOSURIA

(*Posterior Lobe Hypersecretion, Postadolescent, Aneoplastic Type*)

Pathogenesis.—The entire subject of carbohydrate metabolism is one which, even with an increasing knowledge regarding the internal secretions, offers many difficulties in its many divers ramifications. There has been undoubted proof affecting the control or mobilization of the glycogen in the liver by a hormone produced by the insular cells of Langerhans in the pancreas. The summarized conclusion of all experimentors working in this field is that when the proper amount of this pancreatic hormone is given into the venous blood and carried to the liver, the urine remains free from dextrose and the blood contains its normal amount of blood-sugar. When this hormone is absent or decreased in amount, abnormal excretion of sugar occurs from the liver into the blood and the urine, and general disturbances of glycogenesis, with marked excess of sugar in the blood and urine are produced. It has also been proved that secretory dyscrasias of the adrenals, the thyroid, and the hypophysis will produce glycosuria and hyperglycemia. These types of glycosuria have been designated adrenalogenic, thyrogenic, and hypophysogenic. Many of the cases of so-called nervous diabetes undoubtedly have their source in one of these ductless glands. These secretory glycosurias will also explain why nervous disturbances, produced by fear, fright, apprehension, trauma, etc., are causes of true diabetes mellitus. Claude Bernard proved in his fundamental experiment of puncture of the fourth ventricle that he could produce a glycosuria, as well as a polyuria. Aschner has demonstrated that similar sugar centers lie farther centrally in the subthalamic region. It is supposed that the stimulus of these puncture glycosurias travels over the sympathetic nerves and affects some of the ductless glands regulating the carbohydrate metabolism, thus producing glycemia. If this conduction is interrupted in the spinal cord, or if the liver is previously rendered free from sugar by giving strychnia, the hyperglycemia will *not* result. Chromaffin tissue is supposed to be the governing functional device through which these impulses are transmitted. Blum believes that they are passed through the suprarenals. Eppinger, Rudinger, and Falta showed that sugar puncture glycosuria was not induced in thyroidectomized dogs, and believe that the thyroid is the most important ductless gland in the production of this indirect glycosuria. Priestly and Falta point out that it is probably the hyperemia in the liver which is most frequently accountable for the unburdening of sugar, due to adrenalin injections. Neubauer says that there is a constant increase of blood-pressure associated with an adrenalin glycosuria. Kohn demonstrated that there was a decrease in the staining of the adrenals to chrome dyes, as well as a decrease in the depressor power of the suprarenal extract following a sugar puncture. He also showed that when the puncture in the ventricle or subthalamic region was done after previous section of both splanchnic nerves, the glycosuria failed to occur and that the staining of the suprarenals to chrome dyes was retained and not decreased. Nishi demonstrated that the left splanchnic nerve supplies both adrenals, while the right gives off fibers only to the right adrenal. Hence, on section of the right splanchnic, the puncture makes both suprarenals deficient in secretion, while, on section of the left, only the right suprarenal suffers somewhat in its adrenalin content. Electrical stimulation of the splanchnics elicits glycosuria. Tscheboksaroff has attempted to demonstrate that the adrenalin content of the blood of the suprarenal vein is increased by electrical stimulation of the splanchnic. Stewart has demonstrated that the amount of adrenalin in the blood is very difficult to estimate; hence conclusions must remain in doubt. The consensus of opinion regarding the puncture glycosuria, however, is that it is explained by afferent impulses conducted along the splanchnic, which lead to an increase of the secretion of the chromaffin tissue of the adrenals. It is supposed that this secretion produces a dissemination of sugar from the liver. Zülzer was the first to propound the view that the adrenalin and the pancreatic hormones have an antagonistic action; that is, that the adrenalin tends to accelerate the liberation of the glycogen from the liver and that the pancreatic hormone increases its mobilization. That hypophyseal hyperfunction of the posterior lobe actually produces glycosuria has been proven beyond a doubt. Whether this acts through the adrenals or the thyroid, or directly upon the liver itself, is not certain. It is more than likely that hypersecretion of the posterior lobe is a factor in stimulating the chromaffin tissue of the adrenals, and in this way has not only a transient, but a persistent and progressive influence upon the continuation of the glycosuria, thus frequently simulating a true diabetes.

Symptomatology.—History: Case XXVII.—Mr. G. W., aged thirty-five, salesman, St. John's Hospital, General No. 1332, April 6, 1915.

Present.—Chief Complaints: (1) *Polyuria, polydipsia, polyphagia,* and *glycosuria;* (2) *rapid loss of weight and strength;* (3) *epileptiform attacks;* (4) *peculiar mental obsessions* and *"brain storms."*

Duration.—Two months.

Course.—(*a*) *Onset:* Sudden. Following an accident during a recent flood, the patient was almost drowned while crossing a stream, when his covered buggy upset and held him in its top under the water for a considerable length of time. He was finally rescued and resuscitated after four hours of continuous artificial respiration and other restorative means. Previous to this time he had been absolutely well and healthy.

(*b*) *Progress.*—Almost immediately following this accident, the patient first noticed a marked *increase in thirst* and in the frequency of urination, noticeable during both night and day. Coincident with this marked polyuria there was a *polyphagia.* He began to *lose weight* slowly—from ten to fifteen pounds monthly for the past two months. Coincident with this there was a decided *decrease in strength* and *flesh.* Shortly after this accident he had the first attack of *epilepsy.* This commenced suddenly, with a distinct *olfactory aura,* which was soon followed by what was described by his wife as a classical epileptic attack, consisting first of tetanic, soon followed by tonic contractures, and frothing at the mouth. The entire seizure was followed by somnolence lasting three or four hours. He has had three or four of these attacks during the past two months. On one occasion the patient had a very peculiar mental attack, in which, according to his wife's statement, he became "absolutely insane." During this attack he attempted to destroy articles of furniture, tried to "beat" one of his children and his wife, and became almost unmanageable for a short length of time. No loss of consciousness or ordinary signs of epilepsy were present during this attack. The patient seemed to be conscious, but absolutely irrational, and to have "unusual strength" and decided increase in mental excitation as compared with his previous weakness and tendency to depression. There were none of the ordinary convulsive movements of epilepsy present at this time, nor was the attack followed by somnolence. Following the attack the patient denied all knowledge of anything that had occurred during the attack. It was very difficult to convince him that he had been at all irrational, and he was extremely repentant and apologetic for his actions during the attack. The polyuria, polyphagia, and polydipsia had been more or less continuous from the onset to the time of observation. *Glycosuria* had been discovered within a week following the accident at the onset of the disease, and this had been present continuously throughout the entire source of the disease. The patient had complained occasionally of headache of a very severe nature, the definite details of which could not be elicited from either the patient or his wife. His wife states that his *mentality* had *changed* very decidedly *into one of moroseness* and *depression,* and at times he had even been very melancholic, sitting for hours without answering questions or allowing himself to be aroused or interested by extreme efforts made by his family or neighbors. His *extreme weakness* and *mental depression* have completely incapacitated him from doing any kind of work during the entire course of the disease to the present time. There have been no symptoms or signs referable to other systems.

Past.—Measles and mumps during infancy. Acute articular rheumatism at the age of fifteen. Malaria at the age of twenty-five. Negative history for venereal disease, typhoid, and scarlet fever.

Personal.—Habits good, with the exception that he is a heavy smoker. Bowels regular. Alcoholism negative until moderate use recently. Patient married, with two healthy living children. One child died of pneumonia in infancy.

Family.—Mother and father living. Three of five children of the family had epilepsy. One sister eunuchoid build, tall, thin. One brother short, acromegalic stature. Mother had "nervous spells." Negative for tuberculosis, cancer, nervous diseases, diabetes mellitus and insipidus.

EXAMINATION.—*General.*—Eunuchoid stature, showing considerable *emaciation. Long bones well developed,* bony markings prominent throughout the entire body. No *disproportion* in the head, hands, or feet. Marked disproportion between the lower length (from symphysis to soles of feet) and the upper length (from symphysis to vertex of skull). *Adipose* tissue *absent* throughout the entire body. Skin relaxed, dry, harsh. No abnormal pigmentation or hair distribution. No skin lesions, scars, edema, cyanosis or dyspnea. No abnormal gait, station or position. *Pulse, slow.* Respiration normal. *Temperature subnormal.*

Regional.—Head, neck, chest, abdomen, all practically negative, with the exception of those positive signs recorded under general examination above. Physical signs of the visceral organs of the chest and abdomen all within the normal. *Genitalia,* well developed. *Reflexes,* normal, slightly exaggerated; pathological reflexes absent.

LABORATORY FINDINGS.—*Urine* (See chart, page 665).—Twenty-four-hour amount from 1,000 to 6,500 c.c. Specific gravity, from 1.025 to 1.030. Reaction, acid. Dextrose positive, twenty-four-hour amount varying from 0 to 15 grams. Albumin negative. Casts, erythrocytes, and leukocytes negative. Acetone and diacetic acid frequently positive.

OBSERVATION IN THE HOSPITAL.—The patient remained in the hospital from April 7 until May 9. During this time his glycosuria was very easily controlled with only moderate dieting. The maximum reached only 15 grams (half an ounce), and partial starvation, such as the withdrawal of one or two meals every few days, would reduce it very quickly to normal. During this time his polyuria averaged from 1,500 to 4,000 c.c. daily, and was also very amenable to diet and intake. He entered the hospital weighing 132½ pounds, and was discharged weighing 140¾ pounds, with marked increase in strength and quite decided improvement in his mental condition. The general depression and discouraged mental state present at the time of entrance had changed into one of hopefulness and encouragement. No epileptiform seizures had occurred during this observation. The polyphagia and polydipsia had disappeared entirely. The future course of the patient was unknown until it was learned that he had entered Barnes Hospital on March 15, 1917, in a state of coma, in which he died the following day. With the permission of the hospital, the following records are appended:

Mr. G. W., admitted in coma, March 15, 1917.

"No history obtained. Brother said patient had diabetes for the last two years. Lately much depressed because of family troubles.

"Patient lying quiet, eyes closed. Slight external strabismus, right eye. Pupils equal, right reacts slowly to light, left does not, but slowly dilates as light is held. Respiration full, 11 to ½ minute, regular. Pulse, 28 to ¼ minute. Strong odor of acetone noted in room. Friction rub in left axilla felt and heard, few fine râles below angle of left scapula. No dullness. Abdomen negative. Bladder not felt, no dullness. Eyeballs very soft.

"*Blood-sugar*—0.63 per cent. (Benedict).

"N. P. N. of blood—36 mg. per 100 c.c.

"15 grams (half an ounce) of sodium bicarbonate in 500 c.c. (17 ounces) of water (distilled) given intravenously.

"15 grams (half an ounce) sodium bicarbonate given intravenously in 500 c.c. (17 ounces) distilled water at 8.30 P. M.; repeated at 11.30 P. M. No relief of symptoms. Patient catheterized about 8.00 P. M.; again at 12.15 A. M. At this time respirations were slower and rattling, heard in throat. Died at 12.25 A. M., May 16, 1917. No autopsy.

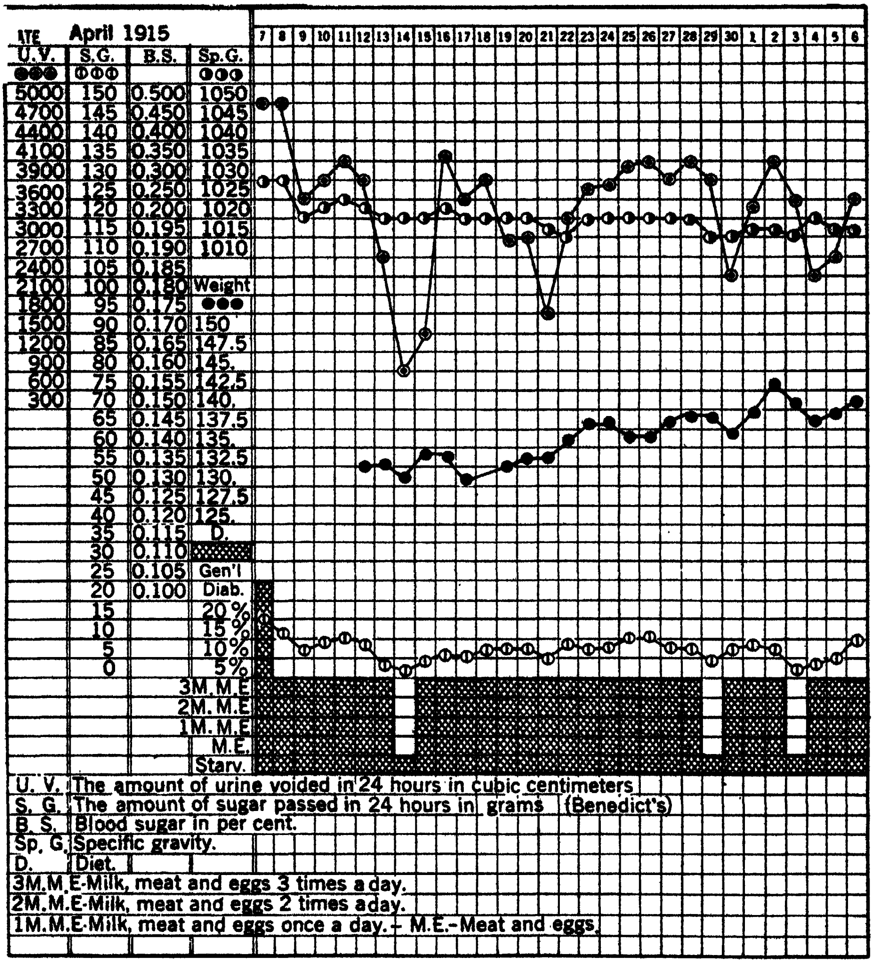
"*Urine.*—3.3 per cent. sugar.

"*Diagnosis.*—Diabetic coma. Pleurisy, left."

Diagnosis.—The diagnosis in this case is a probable *hyperpituitarism involving the posterior lobe, not implicating the anterior lobe.* This diagnosis has for its basis (1) the *combination* of *glycosuria* and *epilepsy,* (2) the etiology of traumata, and (3) the prolonged early course of the disease in which the polyuria was apparently entirely out of relation to the glycosuria. The well-recognized fact that *posterior lobe hypersecretions* are productive of marked polyuria, polydipsia, and polyphagia, with the secondary signs of emaciation and progressive weakness, is well illustrated by this case. That the above syndrome is frequently associated with *glycosuria* is also an accepted fact. The difficulty in the diagnosis in this case, however, is the determination of the actual source of the glycosuria, *i.e.,* whether it was due to a true diabetes mellitus, or whether it was a secondary glycosuria of hypophyseal origin. The writers have taken the ground that it was due to pituitarism, on account of its definite association with epileptiform attacks, occurring during, and only during, the course of the polyuria and glycosuria. The additional mental aberrations and so-called "brain storms" were probably variations of epileptiform manifestations. The termination of this case; however, in which there was an excessive hyperglycemia and death by coma, as ordinarily occurs in true diabetes mellitus, submits this diagnosis to question. Concerning the hyperglycemia, it has been well known that all cases of hypophyseal glycosuria have associated with them a definite increase in blood-sugar, and also at times the definite presence in the urine of acetone and diacetic acid; so this fact in itself would not absolutely outrule the possibility of the hypophyseal origin of both glycosuria and hyperglycemia. Relative to the onset, trauma is an etiological factor of both true diabetes and hypophyseal disease. It has been noted that posterior lobe dyscrasias are more frequently associated with trauma than are other types of pituitarism; but this fact alone would not be an influencing differential point in excluding a diabetes mellitus. Unfortunately, this case occurred before the writers were making careful observations of the pituitary gland, particularly with relation to its size and form and its modifications of metabolism, so that a great many of the very important differential diagnostic facts cannot be included in this report. The epileptiform attacks are the most important clinical manifestation, making the diagnosis of pituitarism probable in this case. Cases reported previously, under the title of *pituitary epilepsy* show the definite connection of some cases of epilepsy with pituitary disease. Of those reported previously, the majority were either of the anterior lobe or of bilobar insufficiency of the hypophysis. None were associated definitely with hypersecretion of the posterior lobe. If this case is one of pituitarism, it must consist of a pure hypersecretion of the posterior lobe, for it has all of the cardinal hormonic signs of such a dyscrasia. There is absolutely no evidence of anterior lobe involvement. Absence of intracranial pressure symptoms would indicate that, at least up to the time of observation, there was no definite pituitary neoplasm.

Complications, Sequelæ, and Associated Diseases.—During the short course of this case under the writers' observation there were no complications, sequelæ, or associated diseases. The marked disturbances of mentality might be considered as a complication, but they have been taken, as will be deduced from the previous report, merely as part of a true pituitarism. The epileptiform attacks were considered as evidence of pressure upon the uncinate gyrus, and the brain-storms and peculiar transitory mental derangement were interpreted as an atypical epilepsy. The terminal condition in this case was one of coma, associated with an acute pleurisy. This termination is not unusual in true pituitary neoplasm of the posterior lobe, although in these cases there are usually much more definite clinical manifestations of intracranial growth.

Clinical Varieties.—This case has been reported to illustrate the clinical type of *pituitary glycosuria.* This has been done more with the view of attracting attention to the possibility of pituitary disease as the cause of atypical cases of so-called diabetes mellitus, than to attempt to dogmatically prove that the glycosuria in this case was really due to hypophyseal disease. It undoubtedly is not a classical illustration, as absolute diagnostic proof is lacking. That there are many such cases, however, which are frequently diagnosed as true diabetes mellitus, is unquestionable. The writers will report the glycosuria existing in a bilobar (or trilobar) case in Section 2. Many other such cases are given in the literature, although none are classed as absolute unilobar cases involving the hyperfunction of the posterior lobe. This particular variety seems to be rather uncommon. At least, in a large series of pituitarisms, consisting of over 200 cases which the writers have observed, this was the best illustration that could be found. The writers feel confident that this clinical variety is justified, and it will probably, with observation directed toward independent hypersecretions of the posterior lobe, be substantiated by many similar positive cases. If this is true, it will definitely demonstrate the two clear-cut clinical varieties of hypersecretion of this lobe of the posterior or pars intermedia lobe of the hypophysis, that is, *pituitary polyuria* and *pituitary glycosuria,* remembering, of course, that there is considerable evidence suggesting that



CASE XXVII. FIG. 1.—URINE CHART OF CASE OF PITUITARY GLYCOSURIA. (*See* page 662.)

pituitary polyuria is a *hypo-* rather than a *hypersecretion* manifestation. It must be remembered that these two cardinal types usually occur with hypersecretions of this lobe. That they are frequently found in bilobar cases in which hyperfunction of this lobe exists, has already been stated, and will be proved by demonstration of definite cases. In these bilobar pituitarisms they are not so strikingly presented as cardinal symptoms, on account of the presence of the many other hormonic signs both of the anterior and of the posterior lobe.

Treatment.—The treatment of hypersecretion of the posterior lobe presenting a decided glycosuria differs very little, if at all, from that of pituitary polyuria. In addition to the ordinary treatment, given in the previous section, dealing with posterior lobe hyperpituitarism, the ordinary, well-recognized **treatment for diabetes mellitus** is probably indicated. This is particularly true late in the course of this disease, when definite changes have probably occurred in the isles of Langerhans or the adrenals, producing true acidosis, similar to that occurring in pancreatic diabetes. The well-recognized **Allen treatment** may become necessary in order to limit the extreme acid intoxication of metabolism which is present in the late course of this disease. The treatment of the *glycosuria* is ordinarily secondary or symptomatic, for the reason that it does not enter into the case as one of the predominating influences affecting the general health of the individual. The *original pituitary dyscrasia* itself must be borne in mind as the prime indication for treatment, and **pituitrin treatment** should be substituted, and, if ineffective, should be followed by **inhibitory treatment,** consisting of **x-ray, radium,** and **surgical interference.**

Prognosis.—The prognosis in this disease differs only in degree from that of dyscrasias of this lobe producing a simple polyuria. The glycosuria variety is undoubtedly of more unfavorable prognosis than the simple polyuria type. This is due to the more progressive and rapid course of those hypersecretions of the posterior lobe having glycosuria as one of their hormonic signs. Those having a simple polyuria are more inclined to fluctuate toward the normal and to have intermittent attacks of hyposecretion, than those having positive hyperglycemia and glycosuria. Whether this is due to an involvement of the infundibulum, or of the posterior lobe alone, is a question. At any rate, this variety is a more definite, progressive disturber of carbohydrate metabolism, and hence, a more unfavorable one throughout its entire course.

SECTION 15

PRE-ADOLESCENT BILOBAR VARIETY

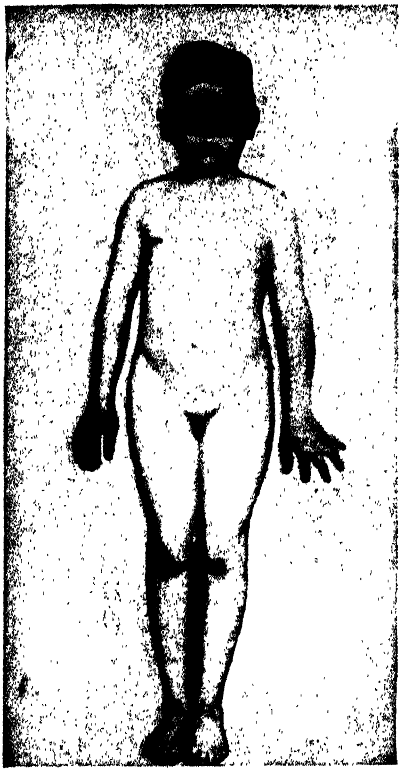
(*Bilobar Hyperpituitarism, Pre-adolescent, Aneoplastic Type*)

Symptomatology.—History: Case XXVIII.—Master H. H., aged nine, schoolboy, St. John's Hospital, General No. 1141.

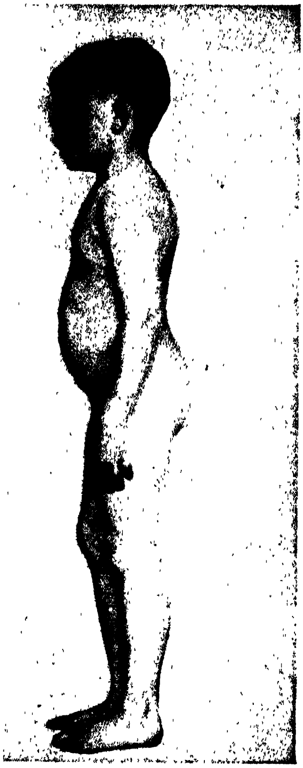
Present.—Chief Complaints: (1) Frequent *recurrent attacks of coryza, associated with asthma;* (2) frequent *severe headaches;* (3) *"general nervousness."*

Duration.—From the age of three or four.

Course.—As a baby the patient was a full-term child, well developed, with no abnormalities of body-proportion. He was of an exceptionally bluish or purplish color at the time of birth, which continued for twenty-four hours after delivery. Two days after birth he developed a slight cough, with excessive mucous discharge in the throat, which required frequent swabbing out. This continued for five days, but no other later signs of respiratory or of cardiac involvement, such as dyspnea or cyanosis, occurred. As a child he was exceptionally strong for his age. His growth was rapid, and there was no delayed dentition, locomotion or gastric symptoms during babyhood. At the age of nine months he contracted a hoarseness, which came on very suddenly, without evidence of cold or coryza. This continued for a few days, then disappeared. At the age of fourteen months he contracted whooping-cough, which lasted four or five months. Since that time he has been subject to *colds* and asthma every winter. In the summer he is usually free from all complaints and symptoms. Since he has been able to run about, his mother has noticed during these attacks of cold that on the slightest exertion the patient easily becomes *breathless,* compelling him to rest. At one time, after walking two blocks, the patient had to be carried home on account of dyspnea and excruciating pain beneath the sternum. This is the only instance of severe pain accompanying these attacks. Cyanosis never accompanied this thoracic distress. He has been frequently examined for tuberculosis, with negative opinions for such disease. On exertion he now notices a sensation of fullness, pressure and "stuffiness" in the throat. He gives no history of difficulty in swallowing, or of enlarged tonsils or other lymphoid tissue. For the past year he has had a feeling of weight and fullness in the frontal region, accompanied by headaches. Three months ago the patient was vaccinated for smallpox, and a month or six weeks following vaccination had a general eruption over the body, in the form of vesicles, which developed into slight pustules, with crested apices, desquamating by scales. Following this he developed pains in various portions of the body, in the bones, joints, abdomen, etc., and extreme weakness. He has been out of school for six weeks, and his mother has noticed that while continuing his lessons at home, he grows very tired and complains of a fullness in the head, which disappears after a short rest. At present he is well developed and nourished and is able to be about without signs or symptoms of any kind.



CASE XXVIII. FIG. 1A.—NOTE SHORT, STOCKY MAKE-UP, WITH UNUSUAL MUSCULAR DEVELOPMENT, SQUARE HEAD, PROMINENCE OF FEATURES, AND ABSENCE OF ADIPOSITY.



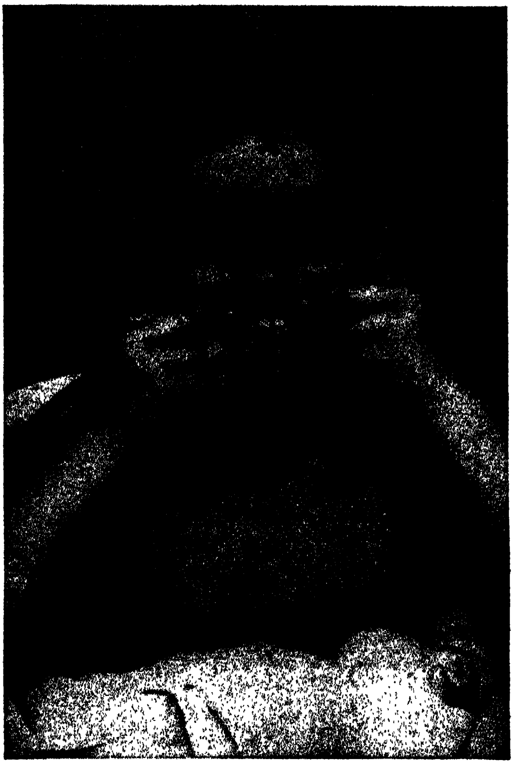
CASE XXVIII. FIG. 1B.—NOTE MANDIBULAR PROMINENCE.

Past.—Whooping-cough. Possibly measles. Vaccinia (?).

Personal.—Appetite good. No insomnia. Bowels regular. Marked nervousness.

Family.—Father, typical acromegalic. Mother, hypothyroid individual.

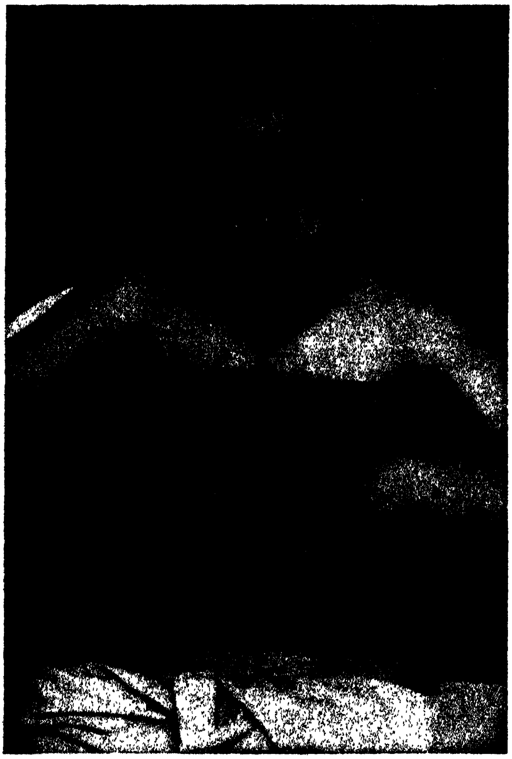
EXAMINATION.—*General.*—Boy nine years old, with marked *genu valgum. No adiposity; musculature unusually developed.* Abdomen and *breast* well *developed.* No secondary sexual characteristics. *Head* *unusually large,* features prominent. Remainder of the body well proportioned. Long bones *not* well developed, but *rather thick* and *stocky;* short and flat bones *well developed. Hands pudgy, short.* Nails do not take up the entire ends of the *fingers.* Head *square;* nose slightly depressed at the angle; lips pouting; jaw well developed. Teeth all present. Upper *teeth separated,* no overcrowding of the lower teeth. Neck rather short and thick; no fullness about the clavicles or upper sternum. Weight, 55 pounds; height, 53½ inches (136 cm.); from vertex to symphysis, 27½ inches (70 cm.); from symphysis to soles of feet, 26 inches (66 cm.); length of femur, 15 inches (38 cm.); lower leg, 15 inches (38 cm.); humerus, 9½ inches (24 cm.); forearm, 9 inches (23 cm.); circumference of head, 21¼ inches (53 cm.); at nipples, 25¾ inches (65 cm.); on expansion, 27½ inches (70 cm.); at hips, 27½ inches (70 cm). Color fair; skin well colored, of a normal pink, mucous membranes especially well colored, scleræ clear. No pigmentation. One pigmented angioma, no other skin lesions or scars. No edema, cyanosis, or dyspnea. Skin rather thin and velvety. No abnormal gait, station, or position. Pulse, slow, regular, equal, symmetrical, low volume and



CASE XXVIII. FIG. 2.—NOTE BROADNESS OF FACE, PROMINENCE OF BONY PARTS, LARGE TEETH, AND SEPARATION OF UPPER CENTRAL INCISORS.

tension, good rhythm, no special type. Tendency to Corrigan, pistol shot, and Quincke pulsation. Temperature, 99.2° F. (37.3° C.).

Regional.—Head: Large, square, as described above, slightly irregular, fontanels closed. Eyebrows well developed, eyes deep-set, lower lids puffy. Nose high saddle type. Ears well developed, normal. Face symmetrical. Hair of good quality, not unevenly distributed. Slight tenderness over the frontal sinus. *Eyes:* Deep-set, palpebral slits equal. Pupils equal, react to light and accommodation. Divergence and convergence without nystagmus. Slight lagophthalmus, equal. Lower lids puffy; upper lids free from puffiness and pigmentation. Brows and lashes normal. *Nose:* Saddle type, with marked hypertrophy of both turbinates. Some bilateral obstruction. *Mouth:* Upper teeth *separated* considerably; lower well occluded, not overcrowded. Eruption normal. All teeth present, no defects or evidence of early decay. Mucous membranes free from lesions and pigmentations. Tongue clean, pharynx injected, both tonsils enlarged. *Neck:* Thyroid not enlarged. No abnormal arterial or venous pulsation. Lymph-glands not palpable. *Chest:* Well developed, spine straight. Expansion good, equal, symmetrical.



CASE XXVIII. FIG. 3.—NOTE MUSCULATURE AND SHORT, BROAD CHARACTER OF HANDS, WITH VERY SHORT NAILS, SHORT FINGERS, AND BROAD WRISTS.

No localized obesity, although the covering of the chest and of the entire body is more than normal. Percussion normal resonance throughout; apices not retracted, on a level, bases of lungs a hand-breadth below the scapulæ. Tactile fremitus equal, symmetrical. To thymus percussion (with the head retracted, in the sitting position), no changeable dullness that extends beyond the manubrium. In the lying position (with the head retracted and the body drawn forward), no dullness to either side of the manubrium or over the jugulum. Normal transmission of voice, breath, and whispered sounds. No râles, rubs, or other adventitious sounds in the lungs or pleuræ. *Heart:* Apex-beat extends to the nipple line, in the fifth interspace, very circumscribed, not forceful or heaving. No diastolic shock, thrill, rub or bruit palpable over the precordia, epigastrium, or jugulum. Borders—apex-beat, fourth interspace, left sternal border. Sounds, apex—slow, pure, regular, rather sharp and snappy. Sounds at the base normal, no murmurs. Heart action modified perceptibly by respiration. No abnormal signs over the large vessels of the neck or chest. *Abdomen:* General and visceral examinations negative. *Genitalia:* Right testicle not descended, palpable in the inguinal ring. Left testicle of normal size. Genitalia otherwise negative. *Extremities* and *reflexes,* normal.

LABORATORY FINDINGS.—*Urine.*—(*a*) Single specimen, color light straw, specific gravity 1.015, reaction acid. Faint trace albumin, few leukocytes, dextrose, erythrocytes and casts negative.

(*b*) Twenty-four-hour specimen, 1,000 c.c., pale, specific gravity 1.015, reaction acid. Trace albumin, few leukocytes. Dextrose, erythrocytes, and casts negative.

(*c*) Twenty-four-hour specimen, 720 c.c., color straw, specific gravity 1.025, reaction acid. Trace albumin, dextrose, leukocytes, erythrocytes and casts negative.

Blood:

Hemoglobin	90 per cent.
Leukocytes	7,000
Erythrocytes	4,580,000
Stained smear	normal
Wassermann	negative

Feces.—Following blood-free diet, brown, formed. Mucus, pus, ova, parasites and occult blood negative.

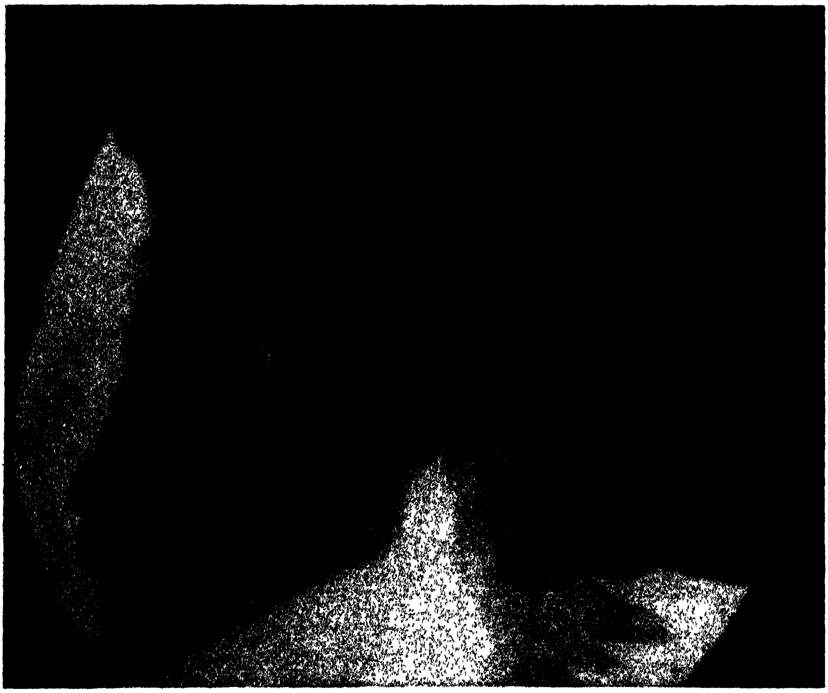
Sputum.—Pneumococci, tubercle bacilli, negative.

SPECIAL EXAMINATIONS.—*Roentgenogram of Head.*—*Sella turcica measures 15 by 16 mm.*

Roentgenogram of Hand.—Absence of closure of the epiphyseal junctures. All carpal bones present, well developed. Metacarpal and phalangeal bones very short, broad and dense. Very slight exostoses of the terminal phalanges.

Roentgenogram of Chest (Upper anterior portion, taken with cone). —Heart slightly enlarged. Shadows to the right of the mediastinum fused, no peribronchial shadows. Distinct shadow on the left side of the sternum, continuous with the heart shadow, extending up to the sternum. This latter shadow is interpreted as cardiovascular, and not thymic. No definite evidence of enlargement of the thymus.

Roentgenogram of Chest (Two months after previous roentgenographic picture).—Taken during attack of asthma. No cervical rib. Thyroid not below first rib. *Entire right lung filled with large* and *small mottled shadows,* with considerable *veiling of entire chest.* Right lower region clearer than the rest of the chest. Marked contrast in the two halves of thorax. Only abnormal shadows on the left side are fusing and some peribronchial thickening opposite the vessel shadows. Note: These shadows were entirely absent in the last examination two months previous. (See description of plate taken at that time.)



CASE XXVIII. FIG. 4.—SELLA TURCICA NOT WELL DEFINED.
Actual measurements in original plate, 15 x 16 mm.

(Three days later.) Complete disappearance of the veiling of the right chest, which was present only *three days previous.* Slightly increased hilus shadows in both sides, over those present in the original plate two months ago.

SUBSEQUENT COURSE.—Close observation for the subsequent two months disclosed the fact that the patient had a *continuous temperature of 99° or 100° F.* (37.2° or 37.8° C.), daily. This temperature was not modified either by exertion or rest. Two attacks of asthma occurred, which were preceded by coryza, with obstruction of the nose and a slight discharge. This coryza would usually be preceded or accompanied by a rather severe headache, which was not localized and was without the symptoms or signs of sinusitis. Frequent *x*-ray examination of the skull and examination by a rhinologist (Dr. C. F. Pfingsten) in the presence of the attacks and during the intervals between them, failed to reveal definite involvement of any of the sinuses. Ocular examination (Dr. E. P. North) was negative for errors of refraction, fundus signs, or abnormal perimeter deviation.

Diagnosis.—The tentative diagnosis in this case is a *suspected* preadolescent bilobar hyperpituitarism. The writers frankly admit that there is considerable uncertainty concerning the diagnosis of pituitarism. They are reporting it to emphasize the necessity of studying these cases during childhood and to attract attention to the possibilities of making early diagnoses in diseases of the pituitary gland. The basis for this suspected diagnosis is as follows: (1) the definite family history of both pituitarism and thyroidism; (2) the unusual apparent susceptibility of this case to infections of the nose and throat, associated with headaches and asthma; (3) the general configuration of the patient: (*a*) the unusually large head, of the hyperpituitary type, (*b*) the unusual development of the long bones, (*c*) the characteristic infantile acromegalic hands and feet, (*d*) the lordosis and tendency to pot belly; and (4) the persistent fast pulse and hyperpyrexia, for which no other cause could be discovered and which have failed to react to any treatment; (5) the detailed makeup of the head: (*a*) the unusually large, hexagonal type of head, with unusually well-placed features, (*b*) the blunt nose and chin, (*c*) the thick lips, and overgrowth of the tissue over all the acral parts of the face, and (*d*) the wide separation of the upper teeth. The hands are of the miniature type, "en large," in having a very wide wrist and short fingers, with tendency to clubbing. Roentgenogram of the hands shows unusual tufting of the terminal phalanges and slight tendency to exostoses. Secondary sexual characters at this age are absent, and consequently there were no changes in the genitalia, as would be expected. The hair distribution is that of the postadolescent variety. There is no evidence that the posterior lobe is involved. The history has been entirely negative for polyuria or polydipsia. The only signs that might indicate a possible posterior lobe involvement are the tachycardia, the hyperpyrexia, and the marked tendency to infections of the respiratory tract, accompanied by typical bronchial asthma.

DIFFERENTIAL DIAGNOSIS.—*Status lymphaticus, hyperthyroidism,* and other *diseases* producing a *continuous low grade temperature* must be given consideration in the final differential diagnosis in this case. It will be noted that all evidence of an enlarged thymus, physically and roentgenologically, has been negative. There is no other evidence of lymphadenoid hyperplasia, in the form of palpable lymph-glands or observable lymphadenoid tissue in the nose, throat, or other portions of the body, which would substantiate such a diagnosis. The history, however, of asthma, associated with dyspnea and, on one occasion, marked substernal pain, is very suggestive and does not allow this disease to be entirely excluded. Pre-adolescent hyperthyroidism is another possibility, which, however, does not present as much clinical evidence to include it as does status lymphaticus. There are absolutely no eye changes, no signs of the thyroid gland itself, no tremor, thyroid heart, or other signs which would make this disease a possibility. Prolonged observation by the writers and others has not been able to include a possible tuberculosis to account for the numerous chest disturbances and the constant hyperpyrexia. During one of these attacks the writers had the opportunity of roentgenizing the patient's chest, at which time a very definite shadow was found involving one-half of the chest. This was at first taken as a possible pleurisy. Aspiration of the chest and the clearing up of this shadow within two days, as proved by both physical examination and roentgenogram, excluded this possibility. After this occurred, it was taken for granted that the condition must have been due to an unusual unilateral congestion of the lungs, present with this type of asthma. The final diagnosis in this case will depend upon very prolonged, careful observation. Its course will probably change sufficiently following adolescence to make the diagnosis unquestionable. The other phases of bilobar hyperpituitarism which will apply to this case will be discussed following the report of the next case, a pre-adolescent hyperpituitarism.

SECTION 16

ACROMEGALY, POLYURIA, AND GLYCOSURIA

(*Bilobar Heteroactive Pituitarism, Postadolescent, Aneoplastic Type*)

Etiology.—The most important point bearing upon the etiology in the following case is the family history. The fact that this case began so early in life would lead one to believe that, if there was any definite etiology, it must have been one of heredity. The early scrofulous condition may possibly have had some effect upon the secretions of the pituitary gland; but more than likely those secretory disturbances evidenced in the family history have more decided bearing. The father was a typical acromegalic. The mother, on the other hand, had a tendency to eunuchoidism, having been of a tall, slender stature. She suffered throughout her life of maturity from migraine, and died early of arteriosclerosis. One brother is obese, without, however, any positive pituitary signs, as obtained from the description. One sister probably has had pituitarism. She has a short, stunted stature, has had very severe headaches and ocular symptoms, and, for a number of years, marked mental and nervous disturbances. One sister had very decided psychoneurosis for a number of years. This very interesting family history coincides well with those which are usually obtained in decided ductless gland dyscrasias, Comparatively few of these cases fail to present fairly definite lineal history showing marked disturbance of equilibrium in the internal secretions.

Symptomatology.—History: Case XXIX.—H. F., aged fifty-two, physician, August 2, 1918.

Present.—*Chief Complaints:* (1) *Polyuria* and *glycosuria;* (2) *exhaustion, mental* and *physical;* (3) *ocular disturbance;* (4) *extreme mental instability,* loss of concentration and memory, decreased capacity, both mental and physical; (5) suspect atypical *renal complex.* Pain referred to the hip and internal portion of the thigh.

Duration.—Forty years.

Course.—(*a*) *Onset:* At the age of twelve the first *frequency of urination occurred.* There was no definite estimation of the amount of urine at this time. Micturition occurred as frequently as every half hour, and nycturia was present.

(*b*) *Progress.*—Two years after this, at the age of fourteen, Dr. Louis Brehmer diagnosed the condition as *diabetes insipidus,* with "neurasthenia torpida." This polyuria continued to the age of twenty, without much fluctuation and without accompanying glycosuria. Adolescence occurred at about the normal age, with marked hypersexuality, which has since been continuously present. There were no changes in other hormonic signs until the age of twenty-two. The patient remembers to have had from early childhood an *insatiable appetite*, which has persisted since. The polyuria was modified more by the *amount of food* taken than by the amount of *liquids*. At the age of twenty-two the patient had an attack of nervous exhaustion, which incapacitated him completely for work for over one year. He was advised to go to Colorado, to a high altitude, for this nervous state. Following two months in this altitude he began to improve, chiefly from the *muscular pains* in the thighs, which were at that time his most distressing symptom. The *polyuria* began to lessen after four months. The patient returned to St. Louis, reëntered medical college, and had one fairly good year. After this nearly all the old symptoms, mental, physical, and the polyuria, returned. A series of *retinal hemorrhages* commenced at the age of twenty-one, and three or four have occurred since that time. "*Migraine ophthalmique*" began at about the age of thirteen (maturity). This peculiar painful, sensitive eye condition was not associated with definite headache, gastric, or abdominal disturbances. Attacks of this "migraine ophthalmic" continued to the age of thirty-seven, when glycosuria was first discovered, since which time it has been entirely absent. The patient had numerous eye corrections for myopia and astigmatism, without benefit. A constant strained condition of the eyes and irritation continued to be marked. Other subjective ocular symptoms have been present ever since, which treatment has been able to relieve. Persistent refractive conjunctivitis was present for six months. Under treatment, and in the high altitude of Colorado, this cleared up within a few weeks. Excoriation of the lids, which had been improved in a high altitude, returned when the patient returned to this climate. Between the ages of twenty-five and twenty-seven there was constant loss of both physical and mental ability, and since that time the condition has remained practically stationary. Numerous symptoms related in the previous history have been more or less present, varying in intensity at different times.

At the age of thirty-seven, during an examination for insurance, *glycosuria* was first detected. *Glycosuria* could *not* be produced by carbohydrate test-meals at the age of thirty-two, and special examinations made for glycosuria by a number of physicians previous to this age were always negative. No sugar-test was made upon the blood until seven years ago. *Hyperglycemia* was present at the age of forty-five. Glycosuria has been present almost continuously for fifteen years, to the present time, and has not responded to the usual diabetic dieting. As high as 8 per cent. dextrose has been present in the urine during a stage of polyuria. Polyuria has corresponded in degree with the glycosuria. After the patient has reduced the sugar in the urine to normal by dieting, considerable tolerance is present for carbohydrates, fruits, etc. The patient has lived upon a tolerant diet, without the production of glycosuria, as long as one and one-half years. Whether or not it has modified the hyperglycemia is not known, as this has been measured only during the last eight or ten years of the course. The addition of meat to this tolerant diet quickly produces glycosuria. The glycosuria, with the accompanying nervous symptoms, fluctuates decidedly, on precisely the same diet, being present under certain conditions, absent under others (the patient taking the same diet). On residing in Colorado four weeks, with no change in diet, but withdrawal of regular work, glycosuria disappeared entirely. Carbon dioxid at this time was below 50 (?). This glycosuria has been present in practically the same amount during the past few years. Diacetic acid and acetone were present on only one occasion, following six days' fast. Estimations of the glycosuria and glycemia, made by Dr. R. B. H. Gradwohl, are given in Table 7.

TABLE 7. GRADWOHL'S ESTIMATIONS OF GLYCOSURIA AND GLYCEMIA

Date	Glycosuria	Glycemia
Aug. 13, 1917	....	0.2
Aug. 16, 1917	....	0.129
Sept. 29, 1917	0.96	0.265
Oct. 17, 1917	....	0.192
Oct. 18, 1917	negative	.....
Dec. 11, 1917	....	0.18
June 28, 1918	faint trace	.....
June 30, 1918	0.3 (trace)	.....

The blood-sugar estimations were taken after twelve-hour fasting, the patient leading an active life of general practice. The first estimations were made while he was on a general diet, the later ones while on a vegetable diet.

Growth was probably arrested at about the age of fifteen or sixteen. There were no special changes in the acral bones of the face, and no definite localized transient enlargement of the hands or feet. Slight stiffness and fullness of the terminal phalanges were noticed for a few hours at times; no puffiness of the backs of the hands, localized sweating, or changes in the soft tissues over the short and flat bones. There has been no marked change in adiposity since young boyhood (adolescence). Nervous instability and lack of concentration have been constant since boyhood. In addition to the constant nervous instability he has suffered an occasional mild brain-storm, in which there was marked loss of concentration, temporary changes in memory, disassociation of ideas, and other disturbances of mentality. The mental exhaustion has been so extreme that it has been described as "actual physical suffering." Supra-orbital neuralgia has been present at intervals during the course. He has a very occasional headache, beginning at the bridge of the nose, extending around the base of the skull, being more marked on the right than on the left. Hypersexuality has been continuously present, and more marked during periods of starvation. No conception has occurred during his long married life. No special estimation of male spermatogenic elements has been made.

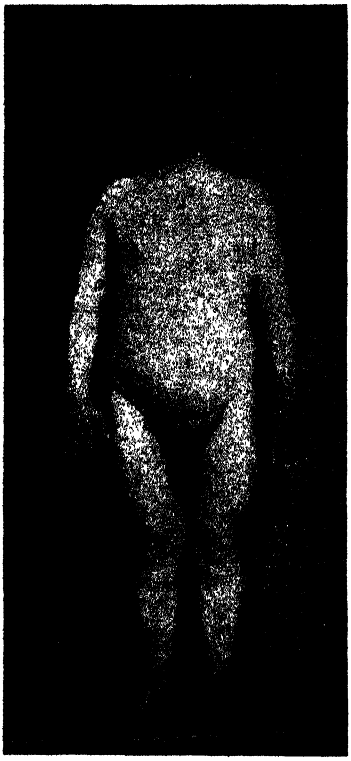
Diseases of Other Systems.—He has had many typical attacks of gall-bladder disease, consisting of extreme abdominal colic, associated with gastric symptoms and fever, but without jaundice. Two roentgenological observers have given the diagnosis of gall-stones on the basis of *x*-ray plates. For five or six years he has had attacks of peculiar renal complex, consisting of colic, radiating down the ureteral region. *X*-ray plates of the genito-urinary system have been absolutely negative for calculi shadows, but demonstrated an enlarged right kidney. Careful cystoscopic examination and ureteral catheterization, with pyelograms, failed to reveal any positive lesion. The urine was usually acid in reaction, heavy, with a precipitate of amorphous crystals, frequently containing for a short time a peculiar greenish sediment, which settled to the bottom. This was said to look like green vegetable fibers. Severe *osteo-arthritis, of hypertrophic variety,* has been present during the past two years. This affected the cervical vertebræ, the knees, and several other joints. The *cervical vertebræ* were *so severely involved* that they *required immobilization* for relief. Treatment of focal infections of the tonsils and teeth relieved the arthritic symptoms almost entirely. The tonsils were not removed, but were reduced to almost imperceptible nodules by fulguration. He has had occasional sinusitis during the past few years, and a probable septic sore throat, contracted from a case of scarlet fever.

Past.—Eczema of scalp present from birth. Peripheral conjunctivitis at the age of two. This was followed by asthenopia, and the patient has had more or less constant ocular disturbance to the present time. He was termed "scrofulous" early in childhood, and given cod-liver oil for years. From five to eight years of age nasal obstruction was considered a part of his scrofula. He was very susceptible to external temperature, particularly cold, in boyhood. This susceptibility left during early adult life, and has returned recently. At the age of ten his father recommended that he take some special exercise to reduce his developing adiposity. Acute articular rheumatism at the age of thirteen. Extreme pain, localized in the heels, at the age of eight. Has painful varicose vein, extending along the right leg, which has enlarged the leg. Retinal hemorrhages, as noted above.

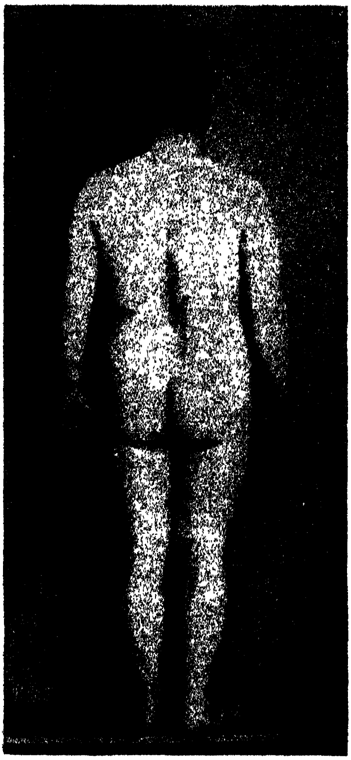
Personal.—Voracious appetite. Moderate use of beer, wine, and seltzer. Tobacco excessively until two or three years ago. Tea and coffee moderately. Hypersexuality present. Venereal disease negative.

Family.—Father of the same build as the patient, not so heavy, of enduring dynamic ability (acromegalic). Mother tall, slender, of moderate height. Mother very nervous, suffered from migraine and had early arteriosclerosis, which probably caused death. Brother inclined to be obese, without definite pituitary signs. One sister very short, of retarded growth. She also has headaches, refractive ocular symptoms, and nervousness. Other sister very stout, short in stature, with peculiar nervous disease (psychoses), which required at times opium for relief.

EXAMINATION: *General.*—Typical acromegalic stature; short, stocky, with marked overdevelopment of musculature. Head large, classical in type, with pituitary nose, pointed chin, and very prominent superior maxillary process. Hands short, stocky, "type en large," slight clubbing of the fingertips, white crescents barely visible. Feet of the same character. Marked abnormal distribution of hair across the abdomen. Eyebrows not bushy, temporal halves thin. Hairline at the temporal region, 2½ cm. from eyebrow; frontal region, 6 cm. Hair on the face not unusually thick, mustache medium. Unusual hair distribution on the lower third of the upper arm; no abnormal amount on the lower extremities. Hair of the axillæ and mons normal. No abnormal pigmentation. Tendency to diffuse erythema about the head, no erythematous spots on the rest of the body. Few small angiomata scattered over the abdomen and chest, no other skin lesions or scars. Varicose vein on the right lower leg. Slight dilatation of venules over an area of the right tibia. No abnormal gait, station, or position. No edema, cyanosis, or dyspnea. Pulse, slow, regular, equal, symmetrical,



CASE XXIX. FIG. 1.—NOTE ACROMEGALIC STATURE, MUSCULAR DEVELOPMENT, LONG TORSO AS COMPARED WITH EXTREMITIES, LARGE, SPADE-LIKE HANDS, AND ABNORMAL DISTRIBUTION OF ABDOMINAL HIRSUTIES.



CASE XXIX. FIG. 2.—POSTERIOR VIEW, SHOWING CHARACTER OF HANDS, MUSCULATURE, AND DISPROPORTION IN MEASUREMENTS.

low volume and tension, no special type. Measurements: Height, 65 inches (165 cm.); from head to symphysis, *34 inches* (86 cm.); from symphysis to soles of feet, *31 inches* (79 cm.); span, *66 inches* (168 cm.); bridge of nose, 2 3/16 inches (5½ cm.); length of humerus, 11 inches (28 cm.); forearm, 9½ inches (24 cm.); femur, 13 inches (33 cm.); lower leg, 13½ inches (34 cm.); circumference of head, 22 inches (56 cm.); at upper maxilla, 21 inches (53 cm.); at lower maxilla, 21 inches (53 cm.); neck, 17½ inches (44 cm.); chest, 39½ inches (100 cm.); abdomen, at navel, 34 inches (86 cm.); symphysis, 36 inches (91 cm.); upper third of thigh, 21½ inches (55 cm.); calf, 14 inches (36 cm.). In the lying position, *no girdle or mons obesity, no* distinct *fullness of the mammæ.* No supraclavicular fat pads, no cushions about the backs of the hands or feet. Mentality, psychoneurotic, well controlled. Temperature, 98.8° F. (37.1° C.). *Blood-pressure, 150/100.*

CASE XXIX. FIG. 3.—LATERAL VIEW OF SAME PATIENT.

Regional.—Head: Hair rather thin, very fine and fluffy. No distinct localized alopecia, some loss of pigment of hair. Marked tenderness over the temporal regions on pressure, some tenderness over the right supraorbital region. Typical pituitary features. Posterior displacement of the ear. Elongation of facial bones as compared with occiput. *Ears:* Air conduction normal, bone conduction normal, Rinne's test negative bilaterally. Inability to locate sounds. *Eyes:* Marked blepharoconjunctivitis, at the temporal side of the right eye. Some mild injection about the conjunctivæ of both eyes. Slight arcus, with clouding of the scleræ in the upper quadrants, more marked in the right. Pupils equal, react to light and accommodation. Muscles intact, no lagophthalmos. Very slight nystagmus on extreme divergence and convergence, in both directions. Eyes deep-set, palpebral slits narrow, probably due to photophobia. Squinting eyelids, probably due to early photophobia. Chronic inflammation of the lid margins (lashes have been pulled). *Nose:* Slight deviation of the septum to the left. Slight injection of the mucous membranes in the lower anterior portion. *Mouth:* Marked separation of the lower teeth, and some irregularity of occlusion. Dentine absent to a large extent in those teeth still present. Probably a third of the teeth have been removed, and the remainder have nearly all been treated or filled. Gingivitis and slight pyorrhea present. Tonsils red, one considerably injected and granular in condition. Pharynx narrow. *Neck:* Short and thick. Thyroid not enlarged, lymph-nodes not palpable. Very slight pulsation in the jugulum and carotids. *Chest:* Unusually well developed, slightly emphysematous (inferior type), anterior-posterior diameter increased. Diffuse hyperresonant note; tactile fremitus equal, symmetrical. Normal transmission of voice, whispered, and breath sounds; no râles, rubs, or other adventitious sounds in the lungs or

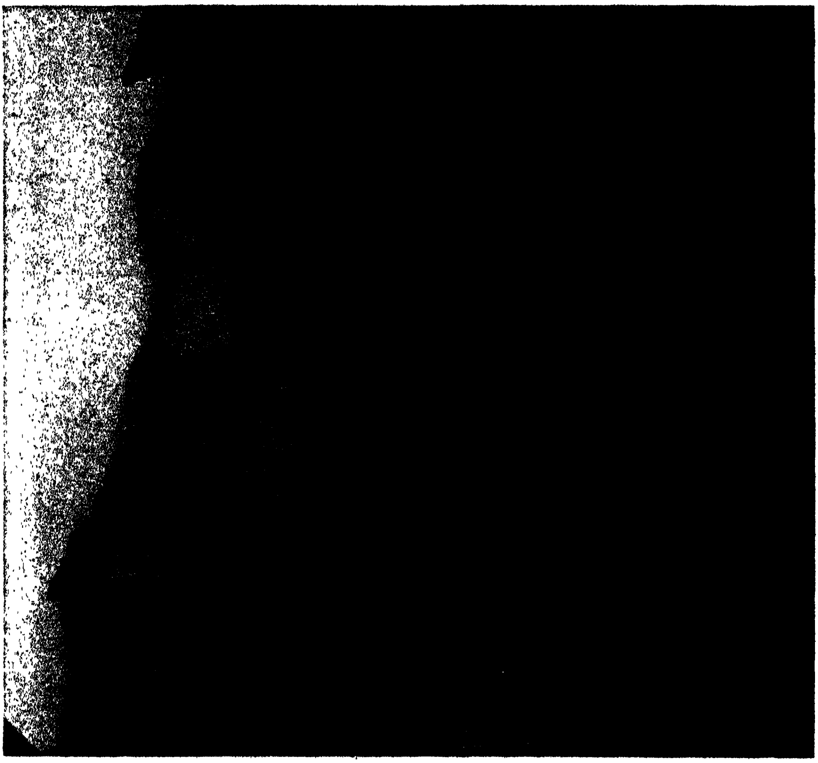
CASE XXIX. FIG. 4.—NOTE BROAD FACE, SHORT, BROAD TEETH, CRUMBLING AND SEPARATION OF UPPER CENTRAL INCISORS.

pleuræ. *Heart:* Apex-beat barely palpable, just within the nipple line, slow, regular, not forceful or heaving. No diastolic shock, thrill, rub, or bruit palpable over the precordia, jugulum, or epigastric region. Borders —apex-beat, fourth rib, midsternal line. Sounds, apex—slow, pure, regular. Slight increase of the second aortic, first tone pure. Second pulmonic also slightly increased, first sound pure. No murmurs, rubs, signs of disassociation or auricular fibrillation. No abnormalities over the large vessels of the chest or neck. *Abdomen:* Symmetrical, retracted. Very slight tenderness over the gall-bladder region and over McBurney's point. No tenderness over the kidneys. No increased resistance, rigidity, tumefactions, or dullness, including deep in the flanks. *Spleen:* Not palpable or enlarged on percussion. *Liver:* Dullness four fingerbreadths above the costal arch. Edge of the liver barely palpable below the costal arch, surface not palpable. Gall-bladder region free from tenderness and tumefaction. *Kidneys:* Not palpable or tender. *Stomach:* Tympany reaches the umbilicus. No splashing sound, peristalsis, or tumefaction. *Colon:* Cecum, ascending colon, transverse, and descending, not palpable. *Suprapubic Region:* Free from tumefaction, dullness, and tenderness. *Genitalia:* Well developed. Testicles normal in size; penis, unerected, about 3 inches (7.6 cm.). *Rectal:* Prostate normal size. Seminal vesicles not palpable. No enlarged hemorrhoidal veins. *Extremities:* Varicosity and dilated venules of the right leg, as noted. Bones and joints normal. *Reflexes:* Babinsky, Chaddock, Oppenheim, Gordon, negative. Achilles and patellars elicited, but not ex-

CASE XXIX. FIG. 5.—NOTE SPADE-LIKE HAND, BROAD WRIST AND PALM, SHORT, STUBBY FINGERS.

aggerated. Cremasterics present, not exaggerated. Abdominals all present, more active than the lower reflexes. Pectorals present, normal. Forearm, biceps, triceps, radio-ulnar, present, not exaggerated. Jaw jerk and Chvostek negative.

LABORATORY FINDINGS.—*Urine.*—Twenty-four-hour specimen, color amber, sp. gr. 1.030, reaction acid. Albumin negative, *dextrose positive.* Very few leukocytes and granular casts. The erythrocyte count was negative.



CASE XXIX. FIG. 6.—NORMAL SELLA TURCICA, MEASURING 10 x 16 mm.

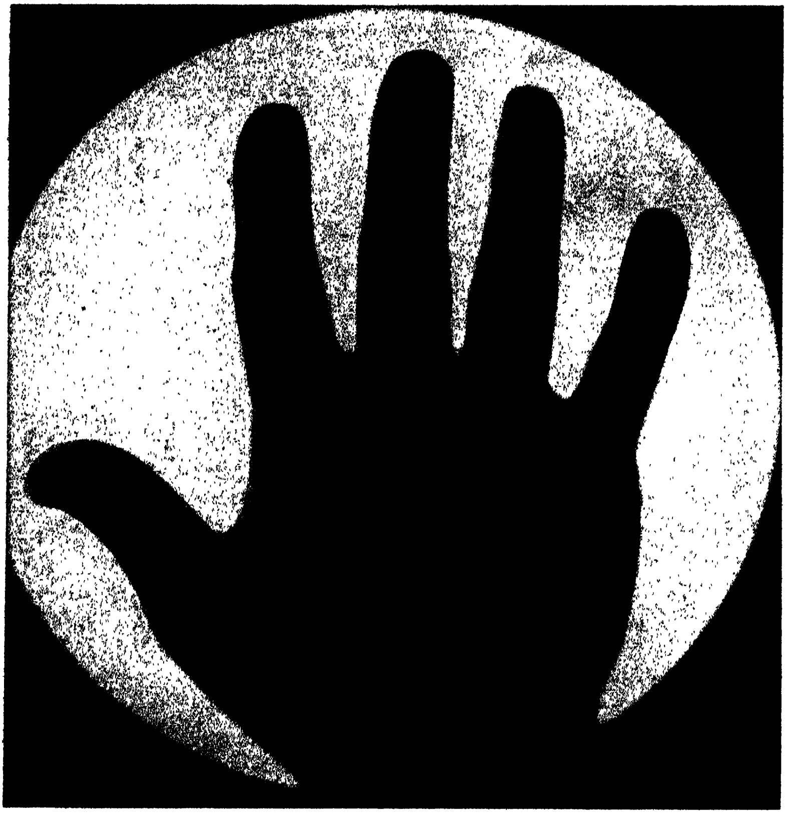
Blood-sugar:

First test (following twelve hours' fasting).... 0.183
Second test (two hours after first and ingestion of 142 grams (5 ounces) dextrose by mouth).. 0.364

SPECIAL EXAMINATIONS.—*Roentgenogram of Skull.*—Sella turcica *normal* in size compared with the remainder of the skull, measuring 10 x 16 mm. Other markings normal.

Roentgenogram of Hand.—Metacarpal and phalangeal bones very *thick, dense,* short. Decided *mushrooming* of the *ends* of the *terminal phalanges.* Exostosis on the terminal thumb phalanx. Hand very short and pudgy.

Diagnosis.—The diagnosis in this case is *postadolescent bilobar heteropituitarism, of the aneoplastic type.* This case is especially



CASE XXIX. FIG. 7.—BROAD, SPADE-LIKE HAND; SHORT, DENSE, AND THICKENED METACARPAL AND PHALANGEAL BONES, WITH MUSHROOMING OF UNGUINAL PHALANGES.

instructive, as it illustrates so many of the important hormonic signs of *hypersecretion* of both the anterior and the posterior lobes, the hyperactivity of which began previous to maturity. It is an unusually good illustration of the following: (1) heteroactivity of the two lobes, presenting a classical syndrome of (*a*) *early pituitary polyuria,* (*b*) subsequent *pituitary glycosuria* occurring in late adult life, and (*c*) continuous increased metabolism during the entire course. The hyperactivity of (2) the *anterior* lobe consists more of the postadolescent variety than that of overactivity of this lobe before maturity. The hormonic signs indicating hyperactivity of this lobe are as follows: (*a*) typical osseous changes, consisting of retardation of the long bone growth, with classical (overgrowth) acromegalic changes in the short, flat, and acral bones. (*b*) Early persistent, continuous hypersexuality. Those pituitary hormonic signs present in this case which may be attributed to (3) *either* lobe are: (*a*) the characteristic headache; (*b*) the pituitary ocular disturbances; (*c*) the classical pituitary mentality and nervous instability.

The onset of the hyperactivity of both lobes of the pituitary gland in this case probably occurred at the age of twelve. While the patient had had from birth numerous nutritive disturbances which were considered due to "scrofula," and which may have had some relation to the pituitarism, the first positive evidence of hypersecretion of this gland consisted of polyuria. This polyuria has been a constant symptom throughout the entire course, during the succeeding forty years. Its early course was associated with a great many nervous disturbances, both cranial and general, and the patient was treated for diabetes insipidus, associated with neurasthenia, migraine, and many other diseases, depending upon the marked fluctuation of the presenting symptoms, for a period of twenty-five years, until the age of thirty-seven, when glycosuria developed. Previous to this age there was absolutely no glycosuria. On account of the polyuria and other symptoms, special tests were frequently made to determine this fact; and one clinician made carbohydrate tests, feeding the patient large amounts of dextrose, in order to definitely determine the sugar tolerance, without being able to produce an alimentary glycosuria. At the age of thirty-seven and during the fifteen years of the course of the disease to the present time, glycosuria, and during the past five years, hyperglycemia, have been added to this picture, converting it into a typical *pituitary glycosuria.* Since this occurred, the majority of the opinions that the patient has received has consisted of a diagnosis of true diabetes mellitus, and a mass of treatment has been directed toward a true pancreatic diabetes. The sugar tolerance has been demonstrated to be very low throughout this entire course of the glycosuria, and in the past five years, during which blood-sugar tests have been made, the blood-sugar has been found consistently high and easily increased by addition of carbohydrates to the diet. A strange and inexplicable fact is that after the patient has reduced his urine sugar to normal, he can take a pure carbohydrate diet, which he is able to tolerate without producing a return of the glycosuria for a considerable time, provided he does not add many proteids, in the form of meats, to this diet. He had one interval of this freedom from glycosuria lasting for one and one-half years. Without changing any other factor, if meats are added to the diet, glycosuria, with an accompanying polyuria, will soon make its appearance, necessitating a renewal of starvation to produce a normal urine. Another very interesting and not yet well appreciated therapeutic hint in this case is the effect of high altitudes upon both a polyuria and a glycosuria, as well as the ocular and constitutional nervous symptoms. On two occasions the patient has observed that a high altitude will decrease the polyuria and allow the urine to return to normal, on a diet which would not have these effects in a lower altitude. A high altitude had the same ameliorating effect upon the nervous disturbance, the subjective, and some of the objective ocular symptoms. A return of these most distressing symptoms has always occurred a short time after the patient has been living in a lower altitude.

The hyperactivity of the anterior lobe, as stated above, probably did not occur at as early an age as that of the posterior lobe. Most convincing proof bearing upon this is the absence of overdevelopment of the long bones, which would have occurred had this lobe been overactive before adolescence. The history states that the patient's height remained practically stationary after he had reached the age of fifteen or sixteen. He feels sure that he has not changed materially in his general development, which might affect the osseous system, the deposition of fat, or the musculature, at least since adolescence. Hypersexuality, probably one of the most reliable hormonic signs of anterior lobe activity, was present, however, from maturity. The physical examination demonstrates the typical signs of acromegaly. The total height of 5 feet 5 inches (165 cm.), which is made up of a marked *increase of the upper measurement,* 34 inches (86 cm.), *over the lower,* 31 inches (79 cm.), demonstrates in itself the over-proportionate development of the short and the flat bones. The upper measurement is produced almost entirely by the size of the vertebra and the flat bones of the head. This produces an excess of 3 inches over the lower measurement, consisting of the length of the long bones, such as the femur and the tibia. This long upper measurement is exactly opposite to that found in eunuchoidism, in which the height of the patient is produced largely by the lower measurement. It corresponds in this case almost to that found in chondrodystrophy, in which the torso measures much longer than the extremities. The circumferences in this case will be noted to be entirely out of proportion to the vertical measurements. The head is unusually large, 22 inches (56 cm.). The chest, 39½ inches (100 cm.), and the pelvis, 36 inches (91 cm.), have unusually large circumferences as compared with the length of these parts. Among the other general characteristics of stature, attention must be called to the peculiar lordosis, producing a marked protrusion of the abdomen in the standing position. This is frequently mistaken for girdle obesity, and in the anterior view photographs might be considered as such. When the patient is lying down, however, there is absolutely no distention of the abdomen, and no unusual adiposity of the mons, abdomen, or breasts. The unusual development of the musculature, as a typical acromegalic sign, is present in this case. The patient's inclination to athletics, having been a skilled acrobat during his early ages, is also one of the constantly accompanying traits of these acromegalic individuals. They are almost always very muscular, even without any inclination to partake actively in physical exercise, and their muscular development is retained, in the great majority of cases, years after they have become very inactive physically. Their low, squatty stature, with the decreased length of the long bones, taken with their musculature, adapts them especially to feats of strength. The unusually strong muscle attachments to the overgrown osseous tuberosities and the short-leveraged long bones give them an unusual advantage in lifting feats that is not present in giants who have the opposite mechanical bone-leverage. The head in this case is especially characteristic. Its large size, the low hairline, the posterior position of the ear, the typical pituitary nose and chin, with the wide separation of the lower teeth, demonstrate almost every detail of the postadolescent pituitary hypersecretion of the anterior lobe. The hands and feet are also very characteristic. Roentgenogram of the hand at the time of observation was more classical than the gross appearance. The mushrooming of the terminal phalanges and the exostosis of that of the thumb, the very short, thick, dense phalanges and metacarpal bones, with their overgrown tuberosities, are particularly instructive. As frequently stated, however, these signs indicate a previous overactivity of the anterior lobe, which need not be present at the time of their observation. The hypersexuality, on the other hand, present from adolescence, throughout the entire course of the time of observation, is conclusive proof that this portion of the pituitary is still overactive.

The nervous and mental signs which might be attributed to either of these lobes, consisting of headaches, ocular signs, and general mental and nervous symptoms, have been, and still are, among the patient's chief complaints. The headaches in this case have been of a typical pituitary variety, although they have not occurred so frequently or persistently as is usual in such a decided pituitarism. The location at the base of the skull, frequently beginning at the bridge of the nose and extending to the occipital region, low in the temporal region, being located persistently unilaterally, associated with subjective ocular disturbances and mental deficiencies, such as loss of memory and disassociation of ideas, is fairly characteristic of pituitary headache. The so-called supra-orbital neuralgia and the very many complex ocular symptoms, both subjective and objective, probably have their origin in the hypophysis. It is true that the patient has errors of refraction and also local lesions of the eyes. The refractive response to treatment, however, and the fact that they improve when other signs of pituitarism are relieved, help to connect them with the secretory disease. The "migraine ophthalmique" described by Charcot is another ocular symptom which in this case probably has a definite pituitary-relationship. It is interesting to note that the attacks of this type of migraine were present during the course of the polyuria and have been entirely absent since the onset and during the course of the glycosuria. This case is an especially good illustration of the peculiar mental and nervous instability present with pituitary dyscrasias. The nervous instability has been present from boyhood, varying from slight functional symptoms to extreme psychoses, completely incapacitating the patient for duties of any kind for over a year at a time. This general neurosis was accompanied in the last fifteen or twenty years by a peculiar physical depression and weakness, concerning which the patient has complained more than of any of the other hormonic signs. The course of this nervous and mental instability has not been progressive, although it has fluctuated with marked recrudescences almost from the onset during childhood. The patient states that it is very difficult to describe the peculiar intracranial, mental subjective disturbances. He states that this is not a true headache or intracranial pressure or vertigo, but consists of a peculiar physical "unreal complex" or "suffering of the head," not relieved by rest, opiates, distraction, or other forms of therapy. Loss of concentration, memory, and marked disassociation of ideas have been present more or less constantly and at times almost completely. For illustration, the patient would be unable to associate the most common object with its name or to tell the location of the street upon which he lived, the name of which when spoken he would recognize very quickly. At times he would have to use the most extreme effort to force himself to do the simplest part of his routine work. He was continually fearful and apprehensive about the outcome of ordinary acts of business to which the normal individual would give no consideration. At times he would be afflicted with mild brain storms, during which, however, he has never lost control of himself or become unconscious; but he was frequently fearful lest he do some conspicuous act without having any intention of so doing. In ordinary conversation he appears to be extremely intelligent and alert, speaking rapidly and precisely. His choice of words is excellent, and, with the aid of notes, he gives a well arranged and orderly chronological history. He has the characteristic loquacious temperament so constantly present in the acromegalic.

Differential Diagnosis.—The differential diagnoses in this case must consider true diabetes mellitus, diabetes insipidus, and the primary psychoneuroses as possible etiological causes for the patient's chief complaints. The writers feel confident that there is no question about the diagnosis of pituitary glycosuria in this case. This was not true of the case (XXVIII) reported in the previous section, in which pituitary epilepsy and glycosuria were reported present. In this case (XXVIII), the history of a previous polyuria, which is so essential to a diagnosis of pituitarism, was absent. Case XXIX, on the other hand, presents the typical early history of posterior lobe dyscrasia, with the positive polyuria existing for twenty-five years *previous to the onset of the glycosuria.* This early polyuria, taken with other positive hormonic signs of pituitarism, fixes the glycosuria in this case as being due entirely to hypophyseal disease. The exact pathogenesis of the glycosuria is another question. It undoubtedly has its origin in hypersecretion of the posterior lobe; but whether this hypersecretion has an inhibitory effect upon this secretion of the isles of Langerhans of the pancreas, or whether it produces a hypersecretion of the chromaffin substance of the adrenals, or acts directly upon the glycogen in the liver, has never been definitely determined. Probably the best substantiated theory deals with its secondary effect through the adrenals, *i.e.*, that a prolonged hypersecretion of this lobe finally produces a decided overstimulation of the chromaffin secretion of the adrenals, which in turn overbalances the antagonistic hormone from the isles of Langerhans, and in this way liberates an abnormal amount of glycogen from the liver and muscle-tissue. This in turn produces the hyperglycemia and glycosuria and allows the intake of carbohydrates to further disturb the carbohydrate metabolic equilibrium. The fact that there is an unusual amount of sugar in the blood and urine, acetonuria and diaceturia, or even that some of these cases die in diabetic coma, does not alter the etiological diagnosis in this case. Borchardt, in his report of one hundred and seventy-six cases, states that in many cases the diabetes showed the ordinary course and eventually led to death in coma.

Cushing reports a very interesting case of "Gumma of the hypophysis with glycosuria and polyuria, diagnosed as diabetes mellitus."

"Case XLVIII. (Surgical No. 21026.):

"July 14, 1907. E. N. R., a merchant, thirty-two years of age, admitted with the complaint of headaches. He is one of a family of ten healthy children. The father was a diabetic.

"The earlier history is without note. His habits are good. He has been married eight years: he has three healthy children and his wife is pregnant (a healthy child was born three months later).

"*Present History:* Three years ago he had a double otitis media: a mastoid operation was performed without disclosing an abscess. Two years ago he had severe occipital headaches for several weeks, diagnosed as 'meningitis.' Owing to continued intracranial discomforts, he has been unable to resume his occupation.

"Six months ago the headaches were attributed to nasal obstruction, but a septal operation served only to aggravate them. A month later a second attack of otitis media occurred, with rupture of the right drum. Two months ago, after a shaking chill, he had a transient left hemiplegia with great increase of cephalalgia. Since that time, nausea, vomiting, intense headache and vertigo have persisted. His temperature has been subnormal.

"*Physical Examination:* A short, rather over-nourished man, weighing 143 pounds, with a pasty complexion, suffering acutely from cephalalgia. There is slight exophthalmus and a low grade of choked disc. Both ears show old perforations—not discharging: no labyrinthine symptoms. There is subjective numbness of the fingers of the left hand, worse during the intense headaches. The examination is otherwise practically negative. The urine is normal: temperature, 97°; pulse, 70.

"A right temporosphenoidal abscess was suspected.

"July 15, *Operation:* A right subtemporal decompression was performed, with exploration of the tympanic roof and temporal lobe. The dura was very tense. There was a great excess of fluid in the meningeal spaces. The temporal lobe was punctured: the needle entering the ventricle withdrew a large amount of clear fluid. *Operative diagnosis:* Serous meningitis (?).

"The patient made a most satisfactory recovery from the operation, and was discharged July 24, completely free from his former symptoms. He was able to resume his business affairs.

"November 13, 1907. *Readmission:* On a recent life insurance examination sugar was found in the urine, and he returned to the hospital for examination. He has gained 13 pounds in weight. Polyuria and polydipsia have been noticed for the past eight years, with some return of headaches, with mental confusion, a slowed pulse, and a bulging of the area of decompression, which, up to this time, has remained collapsed.

"On *examination,* a definite polyuria is demonstrated: 3,150 to 3,500 c.c. *per diem.* Sugar is present in the urine in considerable amounts (49 to 52.5 grams). There is no acetone nor diacetic acid.

"He responded well to a diabetic diet and was discharged November 30. *Diagnosis:* Diabetes mellitus (?).

"*Subsequent History:* After leaving the hospital he did very well for nine months. In *August, 1908,* there was a sudden return of intense frontal headache, vertigo and vomiting, attributed to dietary indiscretion. He became very drowsy, irrational, and disoriented: there was Cheyne-Stokes respiration, projectile vomiting, thick speech, static ataxia, tremor, incoördination of movements, etc. The polyuria persisted. There was no choked disc. A cardiovascular examination was absolutely negative: no arteriosclerosis of the retinal vessels. He continued in this condition until death, which occurred at his home, *December, 1908.*

"*Postmortem Examination:* The brain, with the pituitary body, was removed and brought to us for study. There is a marked nodular arteriosclerosis of the cerebral vessels. The leptomeninges are thickened. The basal ganglia (the right especially) show lacunæ from old areas of softening. A *syphiloma, large enough to be distinctly visible to the naked eye on section, involves the anterior and intermediate lobes of the pituitary body.*"

Many other hormonic signs of pituitarism referable to the anterior, as well as the posterior, lobe, prove the hypophyseal origin of the glycosuria in Case XXIX. Diabetes insipidus can be differentiated as due to other than hypophyseal disease, on the same ground that has been given under the discussion of glycosuria. The very marked evidence of hypophyseal disease here is shown in the growth and development of the osseous system, the hypersexuality, and the late glycosuria, proving, without the venture of a doubt, that this was hypophyseal polyuria. The relation of the marked mental and nervous disturbances to the pituitary, however, is not so easily proven. A review of a large number of other personally observed cases having similar mental and nervous symptoms, occurring in positive pituitary cases, leads one to suspect this origin of these peculiar nervous complexes. The further fact that there are other very positive hormonic signs of pituitary disease gives the writers considerable confidence in attributing the headache, the neurasthenia, and the disturbances of mentality in this case to decided anomaly of secretion of the pituitary gland. *Without other definite evidence of pituitarism, however, these same symptoms could not be classified as hypophyseal in origin.* That is, the writers do not believe that there is sufficient specific character in these nervous manifestations themselves to be of great importance as referring them to secretory dyscrasias. The mere fact that they occur in a very positive case of pituitarism, and the additional fact that there is no other primary nervous disease or general condition to account for them, however, go far toward classifying them as pituitary symptoms.

Complications and Sequelæ.—It is possible that the glycosuria in this case may be considered a complication instead of a definite hormonic sign of posterior lobe hypersecretion. This depends altogether upon the explanation given for its presence. If it could be proved that the glycosuria is due to secondary disturbance of the chromaffin tissue of the adrenals, it should be considered a complication or sequela. This presents the point of early diagnosis and treatment in hypersecretion of this lobe. If such diagnosis could be made early, and treatment which would have beneficial effects instituted before decided disturbance of equilibrium of many other ductless gland secretions occurred, it would undoubtedly prevent many serious consequences. It is hoped that the careful clinical investigation of these glands will bring forth sufficient information to clear up the ultimate cause of such diseases as late diabetes, diabetes insipidus, hyperthyroidism, etc., which undoubtedly belong to interrelated ductless gland imbalance, but which are not yet established upon a definite enough etiological basis to be of value. If it were proven, for instance, that diabetes and hyperthyroidism had for their original cause some other ductless gland secretory disease, it would very decidedly change the current of investigation and the early diagnosis and treatment of these very serious affections, which to-day are considered largely as primary diseases of the thyroid and the pancreas. In this relation, the psychoneuroses, eye symptoms and lesions, and a great many other secondary changes of function of other organs and tissues, have more than a practical bearing in the secretion of these glands. This is true because there is no question that nearly all of these secondary hormonic symptoms are to-day being treated as primary diseases, for instance, of the eye or the nervous system, and there is very little reference made to pituitary or any other secretory cause for their presence. The scope and far-reaching effect of these secretory diseases are only beginning to be slightly appreciated, and the real extent of their influence is now probably far beyond even a vivid imagination.

Associated Diseases.—The early scrofulous condition in this case was one of the first evidences of nutritional disturbance which might possibly have some relation to the pituitarism. The patient showed a marked susceptibility to infection, which was constantly present throughout the entire course of his disease. Numerous infections of the eyelids, scleræ, ears, joints, bones, gall-bladder, pelvis of the kidney, tonsils, teeth, etc., illustrate very decidedly the marked susceptibility to infection to which particularly the bilobar types of pituitarism are subject. It is interesting to note here that the patient had the symptoms both of gall-bladder and of kidney hilus disease. Evidence of lithiasis was found in one of these organs; from the history and the roentgen examination one would suspect the presence of gall-stones. The writers have frequently mentioned the rôle of these diseases of the pituitary, particularly the posterior lobe, which modifies the metabolism, and consequently the precipitation of salts from the excretory organs, as possibly predisposing factors in the stone-forming diseases. It has been well known that the obese female is more liable to gall-stones than the male or the non-obese woman. Obesity itself must be considered a disturbance of metabolism, and, knowing that the internal secretions regulate metabolism, one can readily see the susceptibility of these cases to such diseases. The relationship to arthritis, too, is one that is worthy of more consideration. Knowing the decided control that the anterior lobe has upon the short and the flat bones, due undoubtedly to its influence upon the deposition and immobilization of calcium salts, its relation to diseases of these bones is probable. Blood chemistry shows the marked change in the cholesterin, creatinin, urea, uric acid, and other elements which demonstrate the marked changes in metabolism present in these diseases. The many arthritic pains, the evidence of chronic hypertrophic arthritis, as well as the extreme myalgic pains over the entire body, probably have some relation to the disturbance of secretions in this case. The retinal hemorrhages in this case are thought to be related to the effect of the posterior lobe or the infundibulum secretion upon the blood-vessel walls and the blood-pressure itself. The writers have two other cases of pituitarism having similar retinal hemorrhages.

Clinical Varieties.—The typical bilobar cases cannot be easily subdivided into different clinical varieties. This is due to the fact that they have so many symptoms referable to both the anterior and the posterior lobes, and that these are so constantly changing from one activity to the other, and from the symptoms of one lobe to those of the other, that they present no predominating striking clinical complaint. They might be considered as were those of the hyposecretions, as cases having multiple constitutional disturbances. The pathogenesis of the hypersecretions, however, having polyuria or glycosuria as one of their chief complaints, has been given somewhat in detail in the previous sections, in which cases illustrating only one of these presenting symptoms were described in detail. In reviewing the literature, it is interesting to see the number of cases of acromegaly with which a glycosuria has been associated.

Salomon reported 2 cases, and Bernstein and Falta, one case, of diabetes with pituitarism. Borchardt collected 176 cases of acromegalia from references in the literature, in which descriptions there existed specific statements as to the elimination of the urine. In 35 per cent. of these cases, diabetes was found. In 8 cases there was an elementary glycosuria. "In many cases the diabetes showed the ordinary course and eventually led to death in coma." In many cases this glycosuria shows a striking independence of the sugar value of the diet. Falta reports 8 cases, in 3 of which the glycosuria did not react in any way to the diet. Schlesinger, Borchardt and Cushing report typical cases in which the glycosuria was present only during the initial stages of acromegaly. In Borchardt's case the diabetes had existed for five years, and later glycosuria could not be produced by injections of 150 grams of grape-sugar. In his series of positive operated cases, Frankl-Hochwart describes 7 cases which gave the picture of true diabetes mellitus, associated with acromegaly.

Treatment.—The treatment of a bilobar case does not differ materially from that of a unilobar case in which the posterior lobe or the anterior lobe alone has been involved in overactivity. It is unnecessary to repeat the **direct pituitary treatment,** which has been discussed in the previous two sections. With regard to the **treatment of the individual symptoms,** such as the polyuria, glycosuria, nervous disturbances, ocular diseases, etc., existing in these diseases, if they can be considered as secondary symptoms of pituitarism, it will be seen how necessary it is to treat the original disease intensively. In those cases in which the glycosuria is extreme, the ordinary treatment for diabetes insipidus as recently revised by Allen, Josling, etc., is indicated. It must be remembered, however, that in hypophyseal glycosuria, very early and prophylactic treatment of these hypersecretions might prevent entirely such a late complication or sequel, as is evidenced in the postadolescent extreme glycosuria present, for example, in the case herewith reported.

Pathology.—The pathology of this individual case cannot be positively given. That it is not due to a definite pituitary neoplasm is proven rather conclusively by the absence of enlargement of the sella turcica and the negative evidence of intracranial pressure symptoms. It will probably fall within that group of cases having a simple hyperplasia of both lobes of the pituitary gland, in which more than likely the posterior lobe is more involved than the anterior. The pathology of other ductless glands, particularly the thyroid, existing in hypersecretions of the posterior lobe, has been given in detail in those sections dealing with independent lobar involvements. The pathology due to hormonic disturbances in other structures and tissues has also been previously described (*see* previous four sections).

LITERATURE

Abel and Macht. Histamine and Pituitary Extract. Jour. Pharm. and Exper. Therap., Baltimore, 1919, xiv, 279-293.

Aschner. Über Folgeerscheinungen nach Exstirpation der Hypophyse. Wien. klin. Wchnschr., 1910, xxxii, 572. *Also:* Demonstration of Dogs after Extirpation of the Hypophysis. (Demonstration von Hunden nach Exstirpation der Hyphophyse.) *Ibid.*, 1909, xxii, 1730.

Bab, H. Die Hypophyse als Regulator der Diurese und des spezifischen Gewichts des Harnes. (The Hypophysis as Regulator of Diuresis and the Specific Gravity of Urine.) Münch. med. Wchnschr., 1916, lxiii, 1685, 1721, 1758.

Barker and Hodge. On the Control of Diabetes Insipidus by means of Hypophyseal Extract in a Multiglandular Endocrinopathy. Endocrinology, Oct.-Dec., 1917, i, No. 4, 427.

Barker and Mosenthal. On the Control of Symptoms of Diabetes by Subcutaneous Injections of Extracts of the Hypophysis Cerebri (Pars Posterior and Pars Intermedia). Transactions of the Association of American Physicians, 1917, xxxii, 233.

Benda. Contributions to the Normal and Pathological Histology of the Human Hypophysis Cerebri. (Beiträge zur normalen und pathologischen Histologie der menschlichen Hypophysis cerebri.) Berl. klin. Wchnschr., 1900, xxxvii, 1205-1210.

———— Pathological Anatomy of the Hypophysis. (Pathologische Anatomie der Hypophysis.) Handb. d. path. Anat. d. Nervensystems, 1904, ii, 1418-1439.

Bernard, Claude. Lectures on Diabetes. (Vorlesungen über Diabetes.) 1878.

———— Leçons sur les propriétés physiologiques et les alterations pathologiques des liquides de l'organisme, Paris, 1858, i.

Bernstein and Falta. The Action of Adrenalin, Infundibular Pituitrin, and Glandular Pituitrin on the Respiratory Metabolism. (Ueber die Einwirkung von Adrenalin, Pituitrinum infundibulare und Pituitrinum glandulare auf den respiratorischen Stoffwechsel.) 29 Kongr. f. innere Med., 1912, 536.

Biach. Two Cases of Diabetes Insipidus. (Zwei Fälle von Diabetes insipidus.) Berl. klin. Wchnschr., 1914, li, 380.

Biedl. Internal Secretion. (Innere Sekretion.) Urban u. Schwarzenberg, Wien u. Berlin, 1910.

———— Quoted from Barker and Mosenthal: On the Control of the Symptoms of Diabetes Insipidus by Subcutaneous Injections of Extracts of the Hypophysis Cerebri (Pars Posterior and Pars Intermedia). Jour. Urol., Oct., 1917, i, No. 5.

Blum. Diabetes of the Suprarenal Capsule. (Ueber Nebennierendiabetes.) Deutsches Arch. f. klin. Med., lxxi, 1901 and Arch. f. d. Ges. physiol., xc, 1902.

Bollinger. Dwarfism and Gigantism. (Ueber Zwerg- und Riesenwuchs.) Samml. gemeinwiss. Vortr. Virchow u. v. Holzendorf, Nr. 455, Berlin, 1895.

Borchardt, L. Hypophyseal Glycosuria and Its Relation to Diabetes in Acromegalia. (Die Hypophysenglykosurie und ihre Beziehung zum Diabetes bei der Akromegalie.) Ztschr. f. klin. Med., 1908, lxvi, 332.

Brissaud and Meige. Infantile Type of Gigantism. Jour. de méd. et chir. prat., 25 Janv., 1895. (Type infantile du gigantisme.) N. iconog. de la Salpêtrière, 1904, xvii, 165-172. *Also:* Rev. neurol., 1904, xii, 191-194.

Camus, J., and Roussy, G. Compt. rend. Soc. de biol., Paris, 1914, lxxvi, 773 and 877.

———— Diabete insipide et polyurie dite hypophysaire. Presse méd., Paris, 1914, xxiii, 517.

Polyurie experimentale par lésions de la base du cerveau; la polyurie hypophysaire. Compt. rend. Soc. de biol., Paris, 1913, lxxv, 628.

Presse méd., 1915, xlvi, 517.

Cavazzini-Bergamo. Du casi de tumore dell' ipofisi con sindrome acromegalica curati con e raggi X. Riforma méd., 1920, 162.

Chiasserini. Lesioni experimentali dell' ipofisi. Policlin., Rome, 1918, xxv, sez. chir. 97.

Claude and Lhermitte. The Infundibular Syndrome in a Case of Tumor of the Third Ventricle (Le syndrome infundibulaire dans un cas de tumeur du troisième ventricule). Presse méd., Paris, 1917, xxv, 417.

Clay. Lancet, London, 1889, lxvii, Part I, p. 1188.

Cow, D. Histamine and Pituitary Extract. Jour. Pharm. med. Exper. Therap., Baltimore, 1919, xiv, 275-277.

Crowe, Cushing and Homans. The Pituitary Body and Its Disorders: Incidence: Anterior lobe insufficiency producing obesity, p. 13 and note at bottom of page.

Cushing. The Pituitary Body and Its Disorders. Incidence: Cases XXVI and XXXVI, p. 238.

——— *Ibid.* Incidence: Autopsy findings on gigantism, pre-adolescent hyperpituitarism with giant overgrowth. Enlarged sella, containing cystic struma, p. 162. Case Report XXXII.

——— *Ibid.* Incidence: Gumma of the hypophysis with glycosuria and polyuria, diagnosed as diabetes mellitus, p. 263. Case XLVIII.

——— Concerning Diabetes Insipidus and the Polyurias of Hypophyseal Origin. Bull. Mass. Med. Soc., Medical Communications, xxiv, Part I, 1913, xxv. *Also:* Bost. Med. and Surg. Jour., 1913, xxiv.

Ebstein. Deutsch. Arch. f. klin. Med., 1909, xcv, 1.

Eckhard. Beiträge z. Anat. u. Physiol., 1869, iv, 1, 153; 1870, v, 147; 1872, vi, 51.

Eichorst. Corr.-Bl. f. schweiz. Aerzte, 1888, xviii, 393.

Eppinger, Falta and Rudinger. The Reciprocal Effect of the Glands of Internal Secretion. (Ueber die Wechselwirkungen der Drusen mit innerer Sekretion.) Ztschr. f. klin. Med., 1908, lxvi, 1-52. II Mitteilung. *Ibid.*, 1909, lxvii, 380-398.

——— The Antagonism between the Sympathetic and Autonomous Nerves in Internal Secretion. (Ueber den Antagonismus sympathischer und autonomer Nerven in der inneren Sekretion.) Wien. klin. Wchnschr., 1908, xxi, 752-753.

Erdheim and Stumme. Concerning the Changes in the Hypophysis during Pregnancy. (Ueber die Schwangerschaftsveränderung der Hypophyse.) Beitr. z. path. Anat. u. z. allg. Path., 1909, xlvi, 1-132.

Falta. Cases of Diabetes Insipidus Treated with Pituitrin. (Drei Fälle von Diabetes insipidus, mit Pituitrin behandelt.) Wien. med. Wchnschr., 1915, xlv, 1861-1863.

Falta and Meyers. The Ductless Glandular Diseases. Incidence: Gigantism due to polyglandular hypersecretion, p. 441, 1915.

——— *Ibid.* Observations XXXVII and XXXVIII, p. 323.

Farini and Ceccaroni. Action of the Hypophysis upon the Elimination of Hippuric Acid. (Influenze degli e stratti ipofisari sull' eliminazione dell' acido ippurico.) Gazz. d. osp., Milano, 1913, xxiv, 879-882.

——— Arterial Pressure and Diuresis in the Treatment of the Hypophysis. (Pressione arteriosa e diuresi nella terapia ipofisaria.) Clin. med. ital., Milano, 1913, lii, 497-514.

Fearnsides. Hypopituitarism, Dystrophia adiposogenitalis, Polyuria and Polydipsia, etc. Proc. Roy. Med., London, Neur. Sect., 1916, ix, 50.

Finkelnburg. Deutsch. Arch. f. klin. Med., 1910, c, 33.

Forschbach. Ztschr. f. klin. Med., 1913, lxxvii, 153.

Forschbach and Weber. Ztschr. f. klin. Med., 1911, lxxiii, 221.

Frank. Relation of the Hypophysis to Diabetes Insipidus. (Ueber Beziehungen der Hypophyse zum Diabetes insipidus.) Berl. klin. Wchnschr., 1912, xlix, 393-397.

——— De Curandis Hominum Morbis, iii, Class V (Profluvia), Ordo I (profluvia serosa), Genus II (diabetes), p. 28, Florence, Coen et Socios, 1832.

v. Frankl-Hochwart. The Diagnosis of Tumors of the Hypophysis without Acromegalia. (Die Diagnostik der Hypophysentumoren ohne Akromegalie.) 16 Intern. med. Kongr., Budapest, 1909.

Frey and Kumpiess. The Action upon the Quantity of the Urinary Output in Persons Treated with Pituglandol. (Die Beeinflussung der Harnausscheidung beim Menschen durch Pituglandol.) Ztschr. f. d. Ges. exper. Med., Berl., 1913-14, ii, 380-396.

Futcher. Tr. Assn. Am. Phys., 1904, xix, 247.

Graul, E. A Case of Diabetes Insipidus Successfully Treated with Hypophysin-Höchst. (Ueber einen mit Hypophysin-Höchst erfolgreich behandelten Fall von Diabetes insipidus.) Deutsch. med. Wchnschr., Leipz. u. Berl., 1915, xli, 1095.

Gee. Saint Bartholomew's Hosp. Rep., 1877, xiii, 79.

Gerhardt. Nothnagel's Spezielle Pathologie und Therapie, 1900, vii, 7.

Herring. A contribution to the comparative physiology of the pituitary body. Deutsch. med. Wchnschr., 1915, xli, 261-280.

Hoppe-Seyler. The Relation of Diabetes Insipidus to the Hypophysis and Its Treatment with Extracts of the Hypophysis. (Ueber die Beziehung des Diabetes insipidus zur Hypophyse und seine Behandlung mit Hypophysenextrakt.) München. med. Wchnschr., 1915, lxii, 1633-1635.

Houssay. The Pituitary Body and Polyuria. Endocrinology, Vol. II, No. 2, April-June, 1918, 94.

Hutchinson. The Pituitary Gland as a Factor in Acromegaly and Gigantism. New York Med. Jour., 1898, lxvii, 341, 450; 1900, lxxii, 89, 133.

Jackson and Mills. An Experimental Investigation of the Pharmacologic Properties of the Active Principle of Commercial Pituitary Extracts, and the Comparative Action of Histamine. Jour. Lab. and Clin. Med., St. Louis, 1919, v, 1-27.

Jaugeas. Contribution nouvelle a la radiothérapie des tumeurs hypophysaires. Jour. de radiol. et d'electrol., Paris., 1919, iii, 508.

Kahler. Ztschr. f. Heilk., 1886, vii, 105.

Kleeblatt. Diabetes Insipidus in Injuries to the Skull. (Diabetes insipidus nach Schädelverletzungen.) Med. Klin., Berlin, 1915, xi, 915-919.

Kohn. Chromaffin Tissue. (Das chromaffine Gewebe.) Ergebn. d. Anat. u. Entwicklungsgesch, 1903, xii, 254.

v. Konschegg and Schuster. Deutsch. med. Wchnschr., 1915, xli, 1091.

Külz. Handbuch der Kinderkrankheiten, 1878, iii, Erste Hälfte, p. 285.

Lancereaux. Thèse de Paris, 1869.

v. Langer, C. Growth of the Human Skeleton in Giants. (Wachstum des menschlichen Skelettes in bezug auf den Riesen.) Denkschr. d. kais. Akad. d. Wissenschr. Wien. Mathnaturw. Kl., 31, 1, 91, 1872.

Launois and Roy. The Relations Which Occur between the Activity of the Genital Glands and the Deviating Development of the Bony Structure. (Des relations, qui existent entre l'état des glands genitales et le developpement devié du squelette.) Compt. rend. Soc. de biol., 10 Janv., 1903, 22; et N. iconog. de la Saltpêtière, 1902.

——— Étude biologique sur les genats. Paris, 1904.

Leschke. Beiträge zur klinischen Pathologie des Zwischenhirns. Ztschr. f. klin. Med., Berl., 1919, lxxxvii, 201-279.

Levi and Franchini. A Contribution to Our Knowledge of Gigantism. (Contribution à la connaissance du gigantisme.) N. iconog. de la Saltpêtrière, 1909, xxii, 449, 566.

Lewis. Hyperplasia of the Chromophile Cells of the Hypophysis as the Cause of Acromegaly, with Report of a Case. Bull. Johns Hopkins Hosp., 1905, xvi, 157-164.

——— A Contribution to the Subject of Tumors of the Hypophysis. Jour. Am. Med. Assn., 1910, lv, 1002-1008.

Luzzato. Diabete insipido da emorrogia nelle neuroipofisi e nel peduncolo ipofisario. Sperimentale. Firenze, 1918, lxxi, 405.

Magnus and Schäfer. The Action of Pituitary Extracts upon the Kidney. Jour. Physiol., 1901-2, xxvii, 9.

Marañon. Diabetes Insipidus. Siglo méd., lxiv, 36. Abstract in Jour. Am. Med. Assn., January 20, 1917.

Marañon and Pintos. Lésion traumatique pure de l'hypophyse. Syndrome adipose, génital et diabete insipide. N. iconog. de la Saltpêtrière, Paris, 1916, xxviii, 185.

Massalongo. Acromegalia. (Sull' acromegalia.) Riforma med., lxxiv, 1892.

MEYER, E. Diabetes Insipidus. (Ueber Diabetes insipidus, etc.) Deutsch. Arch. f. klin. Med., i, 83.

MOTZFELDT. The Pituitary Gland and Diuresis. I. Diabetes Insipidus and Its Relation to the Hypophysis Cerebri. II. Studies on the Action of Pituitary Extract, Especially upon Diuresis, Blood-pressure, and Nitrogenous Metabolism of Relatively Healthy Men. Norsk. Mag. f. Laegevidensk., Kristiania, 1915, 5. R., xiii, 1305-1376.

——— The Pituitary Body and Renal Function. Boston M. and Surg. Jour., 1916, clxxiv, 644-651.

Experimental Studies on the Relation of the Pituitary Body to Renal Function. Jour. Exper. Med., Baltimore, 1917, xxv, 153-188.

NEUBAUER, E. Hyperglycemia in High Pressure Nephritis and Its Relation to Glycemia and Glycosuria in Diabetes Mellitus. (Ueber Hyperglykämie bei Hochdrucknephritis und die Beziehungen zwischen Glykämie und Glykosurie beim Diabetes mellitus.) Biochem. Ztschr., 1910, xxv, 284.

NISHI. The Mechanism of the Normal Sugar (Glucose) in the Blood. (Ueber den Mechanismus der Blutzuckerregulation.) Arch. f. exper. Path. u. Pharmakol, 1909, lxi, 186.

OLAECHEA. Sindrome hipofisiario de origen infundibular. Anales de la Facult. de Med., Lima, 1918, ii, 103.

OLIVER AND SCHÄFER. On the Physiological Action of Extracts of the Pituitary Body and Certain Other Glandular Organs. Jour. Physiol., 1895, xviii, 277-279.

PENTIMALLI AND QUERCIA. Quoted from Barker and Mosenthal: On the Control of the Symptoms of Diabetes Insipidus by Subcutaneous Injections of Extracts of the Hypophysis Cerebri (Pars Posterior and Pars Intermedia). Jour. Urol., Oct., 1917, i, No. 5.

ROEMER. The Hypophysis and Diabetes Insipidus. (Hypophyse und Diabetes insipidus.) Berl. klin. Wchnschr., 1913, i, 2354.

——— The Interaction between the Function of the Hypophysis Cerebri and Diabetes Insipidus. (Die Beziehungen zwischen der Funktion der Hypophysi cerebri und dem Diabetes insipidus.) Deutsch. med. Wchnschr, Leipzig u. Berlin, 1914, xl, 108-111.

SALOMON, H. Interchange of Gases in Basedow's Disease and Acromegalia. (Gaswechsel bei Morbus Basedowii und Akromegalie.) Berl. klin. Wchnschr., 1904, xxiv.

SCHAEFER AND HERRING. The Action of Pituitary Extracts upon the Kidney. Phil. Trans., London, 1908, s. B., cxcix, 1-29.

SCHLESINGER, W. The Relation of Acromegalia to Diabetes Mellitus. (Ueber die Beziehung der Akromegalie zum Diabetes mellitus.) Wien. klin. Rundschau, 1908, Nr. 15.

SCHÜNEMANN. Ein Fall von traumatischen hypophysärer Fettsucht. München. med. Wchnschr., 1920, lxvii, 198.

SCHWENKENBECHER. München. med. Wchnschr., 1909, lvi, 2564.

SEILER, F. Ueber das Wesen des Diabetes insipidus. Ztschr. f. klin. Med., Berl., 1907, lxi, 1.

SIMMONDS. München. med. Wchnschr., 1914, lxi, 27.

Hypophysis und Diabetes insipidus. München. med. Wchnschr., 1913, lx, 127.

——— Ueber sekundäre Geschwülste des Hirnanhangs und ihre Beziehungen zum Diabetes insipidus, München. med. Wchnschr., 1914, No. 4, p. 180.

Ueber Hypophysisschwund mit tödlichem Ausgang, Deutsch. med. Wchnschr., 1914, No. 7, p. 322.

SOCIN. Ztschr. f. klin. Med., 1913, lxxviii, 294.

SPAETHER. Quoted from Moffett and Greenberger: Diabetes Insipidus in Children. New York Med. Jour., Sept., 1917, xcii, No. 12.

STERNBERG. Contributions to Our Knowledge of Acromegalia. (Beiträge zur Kenntnis der Akromegalie.) Ztschr. f. klin. Med., 1895, xxvii.

STEWART. Comment on Prof. Vincent's Article on Recent Views as to the Function of the Adrenal Bodies. Endocrinology, i, No. 2.

STOERMER. Inaug. Dissert., Kiel, 1892.

STRAUSS, H. Spontaneous Alimentary and Diabetic Glycosuria. (Alimentäre spontane und diabetische Glykosurien.) Ztschr. f. klin. Med., xxxix.

——— Glycosuria and Mental Diseases. (Glykosurie and Geisteskrankheiten.) *Ibid.*, xxxix.

TALLQVIST. Ztschr. f. klin. Med., 1903, xlix, 181.

TSCHEBOKSAROFF. The Secretory Nerves of the Suprarenal Capsules. (Sur les nerfs sécréteurs des surrenales.) Russki Vratsch. 27 Juin, 1909, viii, 873. Ref. Jour. de physiol. et path. gen., ii, 962.

UMBER. Nutrition and Metabolic Diseases. (Ernährung und Stuffwechselkrankheiten.) Second edition, 1914.

VAN DER VELDEN AND FARMI. Berl. klin. Wchnschr., 1913, l, 2083.

WEBSTER. Roentgen-ray Treatment of Case of Early Acromegaly. Arch. Radiol. and Electrother., London, 1920, xxiv, 261.

WEIL. Virchow's Arch. f. path. Anat., 1884, cxv, 70.

WILLIS. T. De diuresinimia, ejusque remedio, et speciatim de diabetes, in cujus theoriam et therapiam inquiritur. Opera omnia, pharmaceutice rationalis, Sectio IV, Caput III, Henricum Wetstenium, Amsterdam, 1682.

ZENTMAYER, W. The Eye and Endocrine Organs. Jour. Am. Med. Assn., 1917, lxiv, 1.

ZÜLZER. Investigations in Regard to Experimental Diabetes. (Untersuchungen über den experimentellen Diabetes.) 24 Kongr. f. innere. Med., 1907.

IMPORTANT

THE CONTENTS OF THIS AND ALL OTHER VOLUMES ARE INDEXED IN THE SEPARATELY BOUND DESK INDEX.

The subject you are looking up may be closely allied with another and by using the Desk Index of all ten volumes it obviates the necessity of searching through several individual indexes thus saving your time.

E06193